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THE MOUNT SINAI JOURNAL OF MEDICINE

OLUME 57 NUMBER 1 JANUARY 1990

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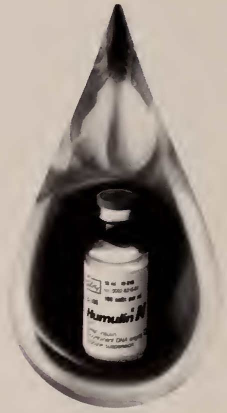

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Editorial

Sherman Kupfer, MD
Co-Editor-in-Chief

The Journal 1990

Readers will note on the masthead in this issue, if they have not otherwise been apprised, that I have joined Dr. David A. Dreiling as co-editor-in-chief of the *Journal*. I have been serving as associate editor since 1987, a brief period on the time scale of this publication. The *Journal* was conceived in 1933 by Dr. Joseph Globus, a giant in the field of neuropathology, and its first issue appeared in May 1934. Dr. Globus served as editor until his death in 1952, when he was succeeded by Dr. Solon Bernstein, whose tenure was cut short by his untimely death. Dr. Lester R. Tuchman, who had already been an editorial staff member for five years, was then named editor and served in this capacity until 1974. He was succeeded by Dr. David A. Dreiling, who had been active on the editorial staff since 1961. Dr. Tuchman has continued to serve as editor emeritus. It is a high honor and privilege to have been given the opportunity to serve the *Journal* as its fifth editor. Needless to say, continuing advice and counsel from Drs. Tuchman and Dreiling will be sought.

Dr. Globus felt that the *Journal* should be a vehicle in which a careful observer could report significant findings in a single case. This report would, thereby, stimulate additional studies and advances in clinical medicine. He noted, too, that an effort would be made to publish lectures delivered at Mount Sinai by prominent clinicians and outstanding investigators. In addition, a popular periodic feature was the publication of *festschriften,* anthologies containing articles from students and colleagues of the individual to whom the issue was dedicated. Dr. Tuchman continued these policies and practices. He reinstituted the publication of clinico-pathological conferences, which ultimately, and unfortunately, could not be sustained. Dr. Tuchman's succinct review, in 1984, of fifty years of material within the covers of the *Journal* is elegant testimony to the tradition of excellence, the hard work, the dedication, and the perspicacity of all who served the Hospital and the *Journal,* particularly Drs. Globus, Tuchman, and Dreiling.

In 1970, the *Journal* changed its name from *Journal of The Mount Sinai Hospital* to its current title, *The Mount Sinai Journal of Medicine,* in an effort to give recognition to the existence of the recently founded Mount Sinai School of Medicine of the City University of New York. The *Journal* recently published an issue dedicated to the twenty-fifth anniversary of the school.

Notwithstanding this brief historical perspective, it behooves us all to wonder, in the face of the overwhelming plethora of medical and scientific journals dedicated to clinical specialties and subspecialties and the basic biomedical sciences, how and why the *Journal* continues to exist. My earliest efforts to examine this question, including a series of discussions with eminent members of our clinical staff and basic science faculty, led me to conclude that there still is a great need for a general medical journal which will attract high-quality, scholarly manuscripts dealing with any and every aspect of the clinical practice of medicine, health sciences research, health care economics, ethics, community medicine, and public health. I confess that all of this has been said by my predecessors, and more eloquently. *Plus ça change, plus c'est la même chose.* Thus, I am left only with the manner by which these continuing objectives can be achieved.

I have invited many members of the faculty at Mount Sinai, and some who are now elsewhere, to join the editorial staff of the *Journal* and/or serve as peer reviewers of the manuscripts which we have been and will be receiving. There has been an almost uniform sense of enthusiasm from this group, and I hope that future issues will reflect this sense of purpose. Our objective will be to provide constructive comments and suggestions by reviewers, and an editorial decision on acceptance for publication, to all authors within 8–12 weeks after receipt of their manuscripts. We hope our reviews will merit quiet contemplation, and that the proffered suggestions will enhance the cherished pride of authorship. If this dialogue can be completed quickly, we can look forward to early publication of accepted manuscripts.

A number of new features will be introduced in an effort to disseminate state-of-the-art knowledge in the clinical and basic sciences. This will be the purpose of the Grand Rounds and Special Seminars series on a broad range of topics presented at Mount Sinai. The first Grand Rounds appears in this issue. Case reports and brief technical and specialty notes will supplement this effort, as will collections of abstracts, introduced in this issue with research reports from a spectrum of subspecialties in the Department of Medicine at Mount Sinai and its affiliates.

What we hope will be a important additional feature in forthcoming issues will be information about new drugs, to include descriptive pharmacology, drug–drug interactions, adverse reactions, and comparative costs.

We hope to stimulate a renewed clinical interest in the knowledge to be gained from selected autopsy studies and thereby promote the frequency of this very important technique for improving the practice of medicine.

A similar effort will be directed to reviewing surgical pathological specimens.

In addition, from time to time, we will continue to publish theme issues devoted to a single broad topic in clinical medicine or the health sciences.

And we will continue to encourage our medical and graduate students to submit manuscripts. All student manuscripts accepted for publication also will be eligible for the annual Student Prize, awarded to the author of the paper judged to be the best of the year in which it was published.

How well our goals of excellence and relevance are achieved can be determined only by our readers. We seek your input in respect to the *Journal*'s appearance, its readability, and, of course, its content. These letters will be given careful consideration by the editorial staff and advisory board. We promise a response. Letters which comment on specific articles, or aspects of specific articles, will be forwarded to the authors, who will be asked to prepare a response that, along with the original letter, will be considered for publication. I look forward to your interest and active participation in the *Journal*'s efforts to serve its readers.

Grand Rounds

Diabetic Ketoacidosis: In Search of Zero Mortality

Alex Stagnaro-Green, M.D.

Diabetic ketoacidosis (DKA) is one of the most dramatic alterations in metabolism, yet one of the most rewarding entities in internal medicine to treat. The patient's return from an initial state of severe acidosis, dehydration, and marked hyperglycemia to a eumetabolic state typically occurs within one day. This is accomplished with modern treatment modalities used in conjunction with an understanding of the pathophysiology of DKA. Unfortunately, the nationwide mortality for this disorder is still 7%, and morbidity is even higher (1).

I present here an overview of DKA in the adult, beginning with a historical perspective on the condition. There follows a review of the precipitating causes and pathophysiology. I also focus attention on treatment, particularly insulin management, and the most controversial modality, bicarbonate replacement. Risk factors associated with an increased likelihood of mortality are identified. Finally, cerebral edema, the most dramatic and perplexing cause of mortality in DKA, is discussed.

A Historical Perspective. Prior to 1922, the treatment of DKA consisted of "rest in bed, special nursing attendance, warmth, evacuation of the bowels by enema, the introduction of liquids into the body, lavage of the stomach, cardiac stimulants, and above all, the exclusion of alkalis" (2). This therapeutic regimen resulted in almost 100% mortality for individuals with type I diabetes (3). The discovery of insulin by Banting and Best in 1921 brought a dramatic breakthrough in the management of the individual in diabetic ketoacidosis. Through a joint venture with Eli Lilly & Company, insulin was commercially available for use in 1923. But the first patient successfully treated for DKA with insulin was a 17-year-old boy treated at Toronto General Hospital in 1922 (3). Although many advances in treatment have occurred since 1921, none has had as profound an impact on lowering mortality as insulin in the early 1920s.

Pathophysiology. The metabolic derangements in patients with DKA result from a marked imbalance in the ratio of insulin to glucagon (4, 5). Specifically, the combination of insulinopenia with concurrent glucagon excess is necessary for the hyperglycemia and excessive ketone production in DKA.

The precipitating event is always insulin deficiency. Interestingly, the insulin deficiency need not be absolute; a relative deficiency of insulin below a minimum concentration required for insulin to perform its metabolic actions is sufficient. The lack of insulin results in three major effects:

- Inability of insulin-sensitive cells to utilize glucose, resulting in hyperglycemia, followed by osmotic diuresis, dehydration, prerenal azotemia, and in its severest form, lactic acidosis.
- Activation of lipolysis, resulting in acetyl CoA production, providing the liver with precursors for ketogenesis.
- Enhanced proteolysis. Muscle breakdown stimulated by insulin deficiency allows for the liberation of amino acids, which are then utilized by the liver in gluconeogenesis, consequently increasing the serum glucose level.

The metabolic changes that occur in the insulinopenic individual work in concert with the effects that glucagon excess has at the hepatic

---

Adapted from a Grand Rounds in Medicine presentation on January 10, 1989 at Mount Sinai Medical Center. From the Division of Endocrinology, Department of Medicine, The Mount Sinai Hospital. Address reprint requests to Alex Stagnaro-Green, M.D., The Mount Sinai Hospital, Box 1055, One Gustave L. Levy Place, New York, NY 10029.

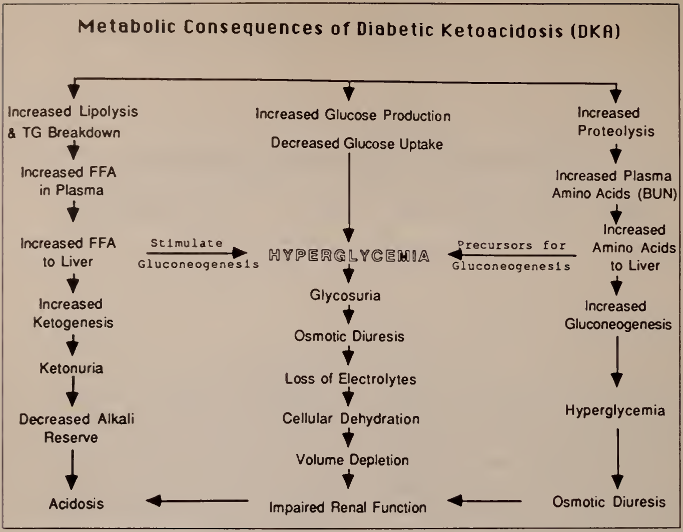
Metabolic Consequences of Diabetic Ketoacidosis (DKA)
Increased Lipolysis & TG Breakdown
Increased FFA in Plasma
Increased FFA to Liver
Increased Ketogenesis
Ketonuria
Decreased Alkali Reserve
Acidosis
Stimulate Gluconeogenesis
Increased Glucose Production
Decreased Glucose Uptake
HYPERGLYCEMIA
Glycosuria
Osmotic Diuresis
Loss of Electrolytes
Cellular Dehydration
Volume Depletion
Impaired Renal Function
Precursors for Gluconeogenesis
Increased Proteolysis
Increased Plasma Amino Acids (BUN)
Increased Amino Acids to Liver
Increased Gluconeogenesis
Hyperglycemia
Osmotic Diuresis

Fig. 1. Altered carbohydrate, lipid, and protein metabolism in diabetic ketoacidosis with resultant water and electrolyte imbalance, impaired renal function, and acidosis. TG, triglyceride; FFA, free fatty acid. *Reproduced with permission* from Kitabchi AE, Murphy MB: Diabetic ketoacidosis and hyperosmolar hyperglycemic nonketotic coma. Med Clin North Am 1988; 72:1549.

level. These effects include glycogenolysis (the liberation of glucose stored as glycogen), as well as gluconeogenesis (the formation of new glucose, from precursors released by proteolysis), and finally ketogenesis (the formation of ketone bodies from the acetyl CoA derived during lipolysis).

In summary, hyperglycemia caused by decreased peripheral glucose utilization and increased glucose production coupled with ketogenesis are the basic metabolic alterations of DKA. This combination of events results clinically in an osmotic diuresis with marked dehydration and a severe metabolic acidosis (Fig. 1). Treatment must interrupt this sequence of events in order to return the individual to a eumetabolic state.

Precipitating Cause. The precipitating cause of DKA is the subject of much discussion in the literature. One of the earliest studies was published by Beardwood and Rouse in 1935 (6). They reviewed the charts of 220 consecutive patients with DKA admitted to their hospital and found 45% had no identifiable cause of DKA. The two most common precipitating factors were infection (17%) and cessation of insulin therapy (7.3%). Since Beardwood and Rouse's study, a variety of centers have published data on common precipitants of DKA. Cohen et al (7), Beigelman (8), and most recently Johnson et al (9) reviewed a total of 422 episodes of DKA. In the compiled data from these three studies, the most common causes of DKA were infection, new onset diabetes, and cessation of insulin therapy. In general, these three etiologies constituted more than 50% of the known precipitating causes of DKA. Other less common etiologies included gastroenteritis, myocardial infarction, pancreatitis, and stroke. No obvious cause was identified in 7% of Cohen's and 18% of Johnson's cases.

Since a precipitating factor can be identified in over half the cases, these studies reinforce the necessity for a thorough search for the underlying cause of the ketoacidosis. This includes a detailed history, which will often reveal alterations in the insulin regimen that resulted in the metabolic decompensation.

Mortality. Although advances have been made in the treatment of DKA, mortality remains a constant problem. Recent statistics reviewing nationwide mortality rates for DKA reveal an average mortality of 7% (1). With an estimated 40,000 admissions yearly for DKA in the United States, this translates into approximately 2,800 deaths annually. Four studies which examined the cause of death in patients with ketoacidosis are reviewed below.

The earliest and largest of the four series

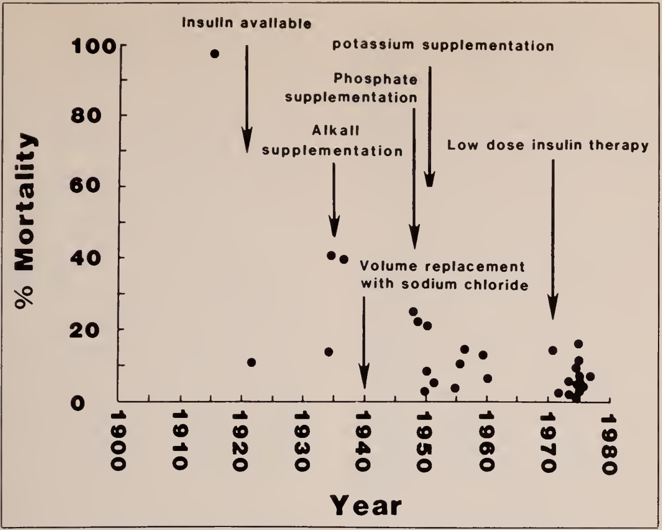

Fig. 2. Milestones in diabetic ketoacidosis therapy plotted against the percentage of mortality. Each black dot represents the mortality percentage for diabetic ketoacidosis reported from individual medical centers in the United States and Europe. Arrows indicate the date at which the therapeutic adjunct was strongly endorsed in the medical literature, and thus the date at which each adjunct came into widespread use. The greatest reduction in mortality occurred following the discovery of insulin in 1922, but a steady improvement has occurred as additional adjuncts in therapy have become available. *Reproduced with permission* from Schade DS, Eaton RP, Alberti KG MM, Johnston DG: Diabetic coma—ketoacidotic and hyperosmolar, University of New Mexico Press, 1981; 5.

was published by Beardwood and Rouse in 1935 (6). In 220 cases of DKA reviewed, there were 52 deaths, an overall mortality of 23.6%. The most common cause of death was infection. Atherosclerosis and uremia were also frequently cited. The researchers also found a strong correlation between age of the patient and mortality, older patients having the greater incidence of death.

Three studies performed more recently (7–9) found a similar correlation between age and increased mortality. Combining the results of these three studies yields an overall mortality of 13%. Furthermore, the major causes of death were cardiac disorders and infection, supporting the findings in the earlier Beardwood and Rouse study. Schade et al recently published a compilation of mortality from DKA at major American and European medical centers. They found the overall mortality to be 7%, with mortality at The Mount Sinai Hospital (New York, NY) of 4% (1).

Clearly, DKA remains a lethal disease, infection and cardiac pathology being the major culprits. It can therefore be concluded that for a patient in DKA, an electrocardiogram should be a routine procedure on admission, as should a chest x-ray and blood cultures. Finally, the older patient has a much higher risk of mortality and therefore warrants special diligence in diagnosis and vigilance in treatment.

Treatment

Insulin. Insulin remains the most important component in the management of ketoacidosis (Fig. 2). Insulin administration results in both decreased gluconeogenesis and ketogenesis and increased utilization of glucose (1). Yet, until the mid-1970s, controversy surrounded the appropriateness of various dosing regimens. What follows is a brief historical review as well as a discussion of the rationale for the current "low-dose" insulin regimen.

In 1923, Wellis Foster published a series reviewing fifteen cases of DKA treated with insulin (10). His recommendation at that early date was to administer an initial bolus of 25 units of regular insulin, and smaller doses every one to two hours. This initial "low-dose" regimen was replaced in the 1940s (11) by much higher dosing regimens. Black and Malins (11) advocated an initial intravenous insulin bolus of 200–400 units of regular insulin, followed by 50 units every 30 minutes until the urine was acetone negative. They based this recommendation on a marked decrease in mortality with this regimen when compared to protocols utilizing smaller insulin doses (28.7% mortality versus 6.6%). Unfortunately, this was a retrospective nonrandomized study, leaving the results open to question.

A variety of factors, including side effects of hypokalemia and hypoglycemia, prompted the reevaluation of "high-dose" insulin therapy (until the 1970s, the conventional therapy). Kitabchi et al (12) conducted a prospective, randomized study of conventional (high-dose) therapy versus low-dose therapy. The low dose consisted of .1U/1b bolus initially, and subsequent doses of 5 U/hour intravenously. Treatment parameters included the amount of time needed to lower the glucose below 250 mg/dL, to raise the pH above 7.3, and to lower the serum acetone below a 1:2 dilution. In all of the comparisons performed, there was no difference between the groups. The only differences found were a higher incidence of both hypoglycemia (25% vs 0%) and hypokalemia (29% vs 4%) in the conventional treatment group as compared to the low-dose therapy group.

Based on the results of Kitabchi's study and of others, low-dose therapy has now become conventional treatment. Furthermore, appreciation of the differential effects of insulin on various metabolic parameters serves to reinforce the appropriateness of the current insulin dosing regimen, and the differential explains the increased incidence of hypoglycemia and hypokalemia in the high-dose regimens. Glycolysis, gluconeogenesis, glycogenolysis, and ketogenesis are all inhibited at insulin concentration of approximately 100 μU/mL. All of these parameters must be inhibited to reverse DKA. Given that the plasma insulin level will increase approximately 20 μU/mL for every unit of insulin given hourly, 5 units of regular insulin given intravenously per hour will therefore provide the sufficient insulin concentration of 100 μU/mL to halt the formation of ketones and excessive glucose production. Consequently, current insulin recommendations for the management of DKA include an insulin drip at 6 units/hour or .1 unit/kg per hour (13). Maximal glucose and potassium uptake both occur at much higher insulin concentrations, explaining the increased prevalence of hypoglycemia and hypokalemia in high-dose insulin regimens.

One caveat, however, is that the physician should not hesitate to increase the insulin infusion when clinically necessary. In particular, marked insulin resistance may occur in individuals with sepsis or myocardial infarctions, and in obese patients with type I diabetes. Such patients are likely to require higher insulin infusion rates. It is, therefore, important to continually reassess the efficacy of treatment in all patients. If, after two hours of treatment, the serum pH and bicarbonate do not increase, the insulin infusion rate should be doubled. Such an increased insulin infusion may produce hypokalemia and hypoglycemia, and thus these parameters will require careful monitoring.

Bicarbonate Therapy. No aspect of treatment of diabetic ketoacidosis has stimulated as much controversy as the question of bicarbonate administration. Not only is there a question about whether bicarbonate is necessary; even advocates of bicarbonate replacement disagree as to the safest and most efficacious route of delivery.

Theoretically, there are good arguments both for and against therapy with bicarbonate. The rationale for intervention with bicarbonate centers on the deleterious effects of metabolic acidosis. These include an increase in cardiac irritability, the negative inotropic effect of acidosis on the heart, and a depressed respiratory drive occurring with severe acidosis. On the other hand, bicarbonate administration may have severe consequences, such as hypokalemia, metabolic alkalosis, and an altered mental status secondary to a continuing low cerebrospinal fluid pH, due to a disequilibrium between the pH of the central nervous system and that of the extracellular fluid.

The controversy surrounding bicarbonate use existed even prior to the availability of insulin. In the 1920s the recommendation was alkali replacement by means of "large doses of bicarbonate soda" (10). In 1974, King et al (14) reported on ten patients with diabetic ketoacidosis who were treated without bicarbonate. Of this group, two patients died from infection; the remaining eight exhibited a steady return to normal pH. The researchers concluded that alkali therapy is only needed when the metabolic acidosis does not respond to therapy with intravenous insulin and fluids.

In 1986, Morris et al published a prospective randomized study designed to examine the effect of bicarbonate administration in medical patients with an arterial pH between 6.9 and 7.14 (15). There were 21 patients enrolled in the study of whom eleven received bicarbonate. Exclusion criteria for the study were severe medical problems

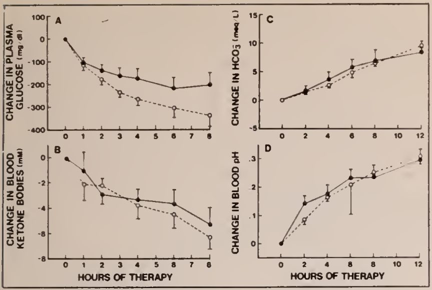

Fig. 3. Changes in blood chemistry values during treatment of patients with diabetic ketoacidosis with or without bicarbonate. Ten patients received bicarbonate therapy (●), and 11 patients received no bicarbonate therapy (○). No significant differences between the treatment and control groups were seen in any variable measured. (To convert mg/dL of glucose to mM, divide by 18.) *Reproduced with permission* from: Kitabchi AE, Ayyagari V, Guerra SMO, and medical house staff: The efficacy of low-dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. *Ann Intern Med* 1976; 84:638.

and age less than 15. Except for bicarbonate, all treatment parameters were identical. The results revealed no difference in the decline of plasma glucose or ketone bodies, or rise in the bicarbonate or pH in the two groups (Figure 3). Furthermore, assessment of cerebrospinal fluid changes in glucose, bicarbonate, pH, or ketone bodies in the two groups revealed no significant difference. The authors concluded that bicarbonate administration in adult patients without serious underlying disorders and a pH between 6.9 and 7.14 was not beneficial.

Despite these studies, bicarbonate use in DKA is still controversial. The controversy is related to the limited number of patients evaluated, the exclusion from study of patients with serious medical problems, and a need to weigh the risks of bicarbonate therapy versus an intuitive sense in physicians that metabolic abnormalities must be treated. Consequently, clinical acumen must be employed.

The current recommendation of the Division of Endocrinology at The Mount Sinai Hospital is that when serum pH exceeds 7.1, bicarbonate almost never needs to be administered. When the pH is between 6.9 and 7.1, only patients with complicated DKA require bicarbonate. Finally, most patients whose pH is below 6.9 should receive alkali treatment; however, the bicarbonate should be given by adding 44 MEq of bicarbonate to a liter of half normal saline and infused over one hour. This extended infusion may decrease the risks of the side effects of bicarbonate therapy.

Cerebral Edema

Ever since the pathologic identification of cerebral edema by Dillon et al in 1936, it has remained a poorly understood cause of mortality in diabetic ketoacidosis (16). What follows is a brief description of the clinical entity as well as a review of its incidence, etiology, and possible treatment implications.

The occurrence of cerebral edema in its severest forms leads to brainstem herniation, coma, and death. On a clinical level, its occurrence is perplexing in that it typically occurs 5–12 hours after therapy has begun, and at a time when the acidosis is resolving and glucose is falling. The mortality rate exceeds 90%, and autopsy findings show flattened gyri and narrowed sulci.

Although the vast majority of deaths due to cerebral edema occur in the pediatric population, it is not unheard of in adults. Furthermore, it has been shown that cerebral edema, on a subclinical level, is present in most patients with ketoacidosis. Clements et al (17) placed indwelling catheters in the subarachnoid space of five adults being treated for DKA. They found both a marked increase in cerebrospinal fluid pressure and an altered mental status 6 hours after initiation of treatment. Later in the course of therapy the cerebrospinal fluid pressures returned to normal, as did the patients' mental status. Furthermore, on CT scans performed on children 7–12 hours after initiation of treatment for DKA, Krane et al (18) illustrated a narrowing of the third ventricle and lateral horns. Hoffman et al (19) extended these results by illustrating, through the use of serial CT scans, that brain edema is present even prior to the initiation of treatment. Treatment therefore is not causative but may exaggerate preexisting cerebral edema.

Taken together, these studies reveal that mild cerebral edema is common in DKA, but its etiology is still speculative. Theories regarding the pathophysiology of cerebral edema include the accumulation of idiogenic osmoles (the accumulation of osmotically active substances in brain cells), activation of the Na+-H+ transport system (a plasma membrane transporter crucial for the control of cellular pH), and a defect in the blood-brain barrier. Unfortunately, little if any data is available to support these theories. Consequently, they offer no therapeutic alternatives.

A recent article by Duck and Wyatt is noteworthy for reviewing all reported cases of diabetic ketoacidosis associated with brain herniation and the finding of an inverse correlation between the rate of fluid administration and time to brainstem herniation (20). Although it is difficult to draw conclusions from such correlational data, a recent abstract reported data which lends further support to less rigorous fluid replacement in the early stages of treatment of DKA. Adrogue et al (21) reported a shorter recovery from DKA utilizing an initial fluid replacement rate of 500 cc/hr of normal saline as opposed to the standard recommendation of one liter per hour. They hypothesized that the decreased fluid administration would also lead to a decreased incidence of cerebral edema.

Taken together, these two studies, along with the increased incidence of pulmonary edema and heart failure seen in the elderly diabetic, are cause for the reevaluation of fluid infusion rates in the treatment of DKA.

Conclusion

The treatment of diabetic ketoacidosis was revolutionized by the discovery of insulin over 60 years ago. Once a uniformly fatal disease, DKA is now a treatable entity, with a nationwide mortality of 7%. The challenge for the future is to refine our treatment, with the goal of further reducing morbidity and eventually abolishing mortality.

Acknowledgments

I thank Sheila Roman, M.D., for review of the manuscript.

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Editorial Note

Who Is Listening?

THE Journal *continues to seek responsible and scholarly articles on and about the health care system and the practice of medicine. The article by Barry Stimmel, which follows, borders on the encyclopedic in its review of many aspects of the system, even touching on research and training in the academic health center. Some will claim that his approach is not focused and his conclusion not supported by studies that show overall health to be better in many other countries that spend considerably less on health care than does our own country. A most compelling reason to publish this article is to bring to the attention of the readers the fact that many sweeping social and financial changes now taking place in the health care system are having an immediate and profound impact in discouraging many young individuals who are most eligible and qualified from choosing a career in the practice of medicine, in medical research, in clinical investigation, and in academic medicine.*

While there are those who will and who have focused on the body count of numbers of students who continue to apply to medical school, students who may in the course of time satisfy the number of available slots in hospitals, clinics, and elsewhere, the real underlying quality of care depends on the capacity and capability of those individuals to synthesize from the patient's history, physical examination, and cost-effective laboratory data the most probable, if not the correct, diagnosis, and then to offer a prescription for treatment which is most likely to cure, or to offer relief, with the least risk of harm. What needs to be done, and what incentives are to be offered, to attract the most qualified and capable individuals who, for their lifetime, will be committed to deliver service to their patients and to their communities, service which is inextricably bound to the continuing study of health and disease? This is no small challenge, and certainly is not to be undertaken by those of faint heart and mind.

Stimmel's article does not address the whole arena of need for qualified practitioners, researchers, and academicians in community medicine, public health, preventive medicine, and the environment. Reordering priorities in the spending of money, never popular to begin with, to expand essential support in many deserving critical areas that surely will affect the quality of life in the third millennium of the common era is yet to be addressed. Perhaps the bells are tolling now—but who is listening?—Sherman Kupfer

The Study and Practice of Medicine in The Twenty-First Century: Ask Not for Whom the Bell Tolls

Barry Stimmel, M.D.

Abstract

Economic forces are rapidly transforming the profile of medical practice. Many of these changes will be beneficial and are long overdue. A number, however, have the potential to adversely affect both physician and consumer. At present, consumers are expressing few concerns; the concerns of physicians are receiving little attention. Consumers are quite content with the possibility of further decreases in medical costs and are relatively unconcerned with the potential decrease in the quality of care that may result or the diminished numbers of physicians entering research careers. If a decrease in quality of care occurs, it will be subtle, not recognized by the public for a number of years. Although the demographics of those entering practice may change, physicians as a group will adjust and survive, and the study of medicine will continue to attract those committed to the provision of health care. Ultimately, it will not be the physician who will "suffer" but the consumer.

OVER the next five years the practice of medicine in this country will continue to undergo a remarkable transformation. Although many factors have served as catalysts, concern over the increasing costs of health care has been dominant. This concern is not unwarranted. Between 1966 and 1986, health care expenditures rose from $39 billion to $458 billion, with a projected increase of $50 billion in 1989. In 1987, health care costs accounted for 11.4% of the gross national product (GNP), compared to 7.5% a decade earlier, and it has been estimated that health care costs will exceed 12% of the GNP by 1990 (1).

Forces for Change. Although a matter of persistent attention by economists, consumer involvement in controlling health care costs was not prominent as consumers' direct costs decreased from 50% of health care spending in 1966 to 27% in 1982 (2, 3). Reimbursement for hospital care followed a similar pattern, third-party payments rising from 77% to 91% of total costs. This shift served as a buffer between patients and the cost of their care. Those paying the bills, however, namely the federal government and the third-party carriers, were less than sanguine.

Quality of Medical Care. Concerns also existed with cost effectiveness and necessity of care provided. Studies consistently appeared in the literature suggesting that the quality of care received varied greatly, depending on availability of hospital beds, geographic region, density of specialists, and type of practice (4–7). In 1988, a survey found only 54% of Americans to be satisfied with their encounters with physicians, 89% feeling that their health care system required fundamental changes in both direction and structure (2).

Comparison of health care expenditures and indices of health care between the United States and other countries is far from favorable. Although the percentage of the gross national prod-

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uct spent on health care in the United States is twice that of Great Britain's and the per capita spending 2.7-fold, some indices of public health between the two countries, such as life expectancy, differ little, whereas others, such as infant mortality, are higher in this country (2, 8).

Another glaring difference is the ability to obtain health care insurance. It has been estimated that the number of people without health care insurance in this country is 37 million—an increase of 25% since 1980 (2, 9). Not unexpectedly, the poor are particularly affected, being three times more likely not to have any health insurance, including Medicaid (10).

Physician Workforce. Until recently, effective reduction in health care costs remained hampered by the perception of a deficit of physicians and the unstated, though implicit, fear of physician refusal to participate in cost reduction measures. Personnel surveys over the past several years have finally put these fears to rest. In September 1980, the Secretary of Health and Human Services (HHS) released a report of the Graduate Medical Education National Advisory Committee (GMENAC) which anticipated a surplus of approximately 98,000 physicians by 1990, 15% of specialties having surpluses as high as 190% (11). Although this report initially met with serious criticism, subsequent studies suggested that GMENAC's projections were too conservative (12). A HHS report exceeded the GMENAC estimates by predicting an increase in physician population per 100,000 from 199 in 1981 to 235 in 1990 and 260 in the year 2000 (13). A study by Steinwachs et al concluded that even GMENAC's requirement for primary care physicians was overstated, suggesting that 20% to 50% fewer primary care physicians would be required because of the rapid growth of alternative health care systems (14). The entry into this country of increasing numbers of foreign medical graduates (FMGs), and the return of many U.S. citizens trained in foreign medical schools, furthered the concept of a physician surplus.

In reality, however, controversy still continues on the magnitude of the surplus and even on whether any surplus of physicians exists. Jacobsen and Rimm, noting attempts to limit the entry into the United States of foreign medical graduates, as well as considerations being given to decreasing class size in medical schools, have estimated the physician surplus to be less than 40,000 in the year 2000 (15). Schwartz and colleagues have also concluded that there will be little or no physician surplus, based on a variety of factors, including the continued "graying" of the population requiring medical care, the increasing strains placed on the health care system by the acquired immunodeficiency syndrome (AIDS), the advances in technology requiring additional physician services, the diminishing entry of FMGs over the past two years, the failure of managed health care to expand at the expected rates, the decreasing hours worked by residents, requiring increasing attending-physician coverage, and the increasing pool of women physicians who are believed to work about 10% fewer hours than men (16). Indeed, Schwartz et al concluded that demand may exceed supply by 7,000 physicians in the year 2000. The reality of manpower needs, however, remains overshadowed by the prevailing public perception that, at present, there are too many physicians, thus allowing, for the first time, competitive market principles to play a role in shaping changes in health care delivery.

Initiating Change. In an attempt to make the consumer more cost conscious, those insuring the costs of health care, realizing that a "buyer's market" exists, initially responded by decreasing available benefits and increasing the codeductibles. This has been partially successful. A public opinion poll taken in 1981 revealed that 55% of those surveyed believed that cost was a major problem in health care. In 1984, 68% held that view. In 1982, 42% of consumers believed that physician fees were usually reasonable; however, by 1984, only 27% felt this way, and only one in five responders believed that physicians had been active in holding down health care costs (17).

Active initiatives surfaced at all levels to decrease health care costs, beginning with the education of students and extending to altering reimbursements for practicing physicians. Investors with venture capital became interested in the medical marketplace, further increasing competition among carriers, suppliers, and institutions. For-profit hospital chains increased their acute-care bed capacity from 55,000 in 1976 to 111,000 in 1984 (1). The escalating cost of obtaining health care insurance began to slow.

Even employers started to become optimistic over their ability to contain health care costs. Of those companies that had delineated specific goals in cost containment, only 18% believed that their objectives could not be achieved. In short, with the exception of a vested interest group—the physicians—contentment seemed to reign, and few voices were raised against the progress being made.

The changes that have occurred and that will continue to occur in health care delivery and reimbursement are based on the assumption that much of the care rendered in our system is inefficient, unnecessary, or inappropriately priced. Although this is likely to be true in many instances, unfortunately the problem is not so simple. Increasing costs are also clearly related to the quality and level of care provided. Showstack et al have shown that the primary cause of rising costs of hospitalized patients was the need for more technically advanced care, such as surgery for acute myocardial infarction, treatment of the acute respiratory distress syndrome, and other intensive treatments to the critically ill (18). These therapies, although able to prolong life, are associated with great increases in costs. As demonstrated by Schwartz, even when all unnecessary care is eliminated, the increase in medical care costs will reemerge unless services related to expanding technologic advances are restricted (19).

The enthusiasm of the consumer, the third-party carrier, and both public and private sectors over these savings has yet to be accompanied by concern over the effects that these changes will have on the practice of medicine or the provision of quality health care. This paper reviews these effects of the changing medical "scene" on both the study and practice of medicine with respect not only to physicians but also to the equally important matter of the quality of care that may ultimately be made available to the public.

The Study of Medicine

The Status of Medicine as a Career. Gaining admission to a U.S. medical school has always been difficult and anxiety-ridden. This, unfortunately, has fostered an unhealthy competition among students interested in the study of medicine, a focus on courses believed to be required or "easy" rather than those intrinsically rewarding, and a general unfavorable undergraduate view of premedical students. Although medical schools have tried to change the image of what is desired in an applicant, they have not been very successful. Recently, through the publication of the Association of American Medical Colleges' report, "General Professional Education of the Physician and College Preparation for Medicine (GPEP)," the importance of a broad-based undergraduate education and the need for inculcating humanism in both undergraduate and medical education have been emphasized (20). This report, widely quoted in professional journals and the media, however, has been accompanied by neither a groundswell of applicants nor revolutionary changes in medical education. In fact, the evidence suggests that undergraduate students, rather than being stimulated to apply for careers in medicine, are losing interest.

The number of applicants to medical schools, which reached a high of 42,624 during the 1974–75 academic year, with an acceptance rate of only 35.3%, has consistently decreased. In 1988, there were only 26,721 applicants to the first-year class, a decrease of 43%. Of these applicants, 60% were accepted. If this trend continues, by 1990 the applicant-position ratio will be 1.5:1, and the first-time applicant-position ratio will be 1.06:1, the lowest in 60 years (21).

Although many qualified students still wish to study medicine, the persistent decrease in the size of the applicant pool is becoming disconcerting. The reasons for this decline, as articulated by undergraduate students, are easily discernible and include (1) impressive indebtedness, resulting from increasing tuition fees accompanied by decreasing federally subsidized loans; (2) perceptions of physicians' loss of independence because of the erosion of fee-for-service and expansion of "contract" medical practice; (3) the ability of graduate study to better meet career objectives; (4) the increasing attractiveness of nonmedical careers; (5) perceptions of increasing physician liability from malpractice claims; and, perhaps the most damaging, (6) discouragement of applications to medical school by physicians (22).

Concern over not being able to meet basic financial needs is most prominent among minority students, who are often from lower socioeconomic groups. Although the proportion of black and other underrepresented minorities has remained relatively stable between 1981 and 1988, there are still far fewer minorities interested in medicine than one would like to see. As documented by the Educational Testing Service, many of the brightest, most capable minority students are tending to choose professions other than medicine (23). The loss of minority candidates is disconcerting, because there is a need not only to establish a healthy heterogeneity of physicians but also to increase medical care to the underserved—and significantly more minority physicians serve in inner cities and in primary care than nonminorities (24).

Economic forces, however, are also adversely affecting students from both middle- and upper-income families. Even these families' income is insufficient to meet the escalating costs of undergraduate and medical school tuitions. In the 1988 applicant pool, the greatest decrease in applicants was among white male applicants, who constituted 70.7% of the pool, as compared to 79% in 1981 (21).

Decreasing federal support for medical education, accompanied by increasing tuition and fees, has resulted in a consistent increase in student indebtedness. The average graduating student indebtedness rose from $19,969 in 1981 to $38,489 in 1988, some individual students owing as much as $100,000 by the time of graduation (25, 26). Although many legislators are in favor of maintaining direct student support through federally subsidized loan programs, the Administration, convinced of the surplus of physicians, continues to chip away at even the relatively high-interest loan programs.

Each year the Administration forwards a number of proposals that, if approved, would seriously impair students' abilities to completely finance their education. These proposals have included termination of scholarships for students with exceptional financial need; elimination of all National Health Service Corps Scholarships; and restriction of Health, Education Assistance Loans (HEAL) and Guaranteed Student Loans, these last two programs currently accounting for 76% of all loans to medical students.

In fact, HEAL is far from a lender-friendly program, having compound rather than simple interest and a repayment schedule commencing within nine months after graduating from medical school or after completing a residency. As demonstrated by Iglehart, a student who borrows $10,000 with a 25-year repayment schedule at 11% interest will repay $169,250 (25). Nonetheless, the amount of money borrowed from this program is considerable, amounting to $285 million in 1985 and $365 million in 1986 (27). As might be expected, the HEAL program is currently experiencing an extremely high default rate, some residents who are still in training and unable to meet their payments owing as much as $100,000.

Fortunately, the recently passed Higher Education Amendments Act of 1986 (S.198\65) will have a generally beneficial effect on federally financed assistance programs, yet student indebtedness will undoubtedly continue to increase.

Student concerns over the economics of a medical career are also not lessened by the realization that the rate of house staff salary increases not only has slowed but, in some institutions, has not met increases in cost of living (28). Income earned after residency in the first year of practice has also remained relatively stable over the past several years, whereas initial professional income has risen in other fields, notably law, where starting salaries in large firms are more than double those of house staff.

This anxiety may ultimately express itself not only in career choice but also in practice patterns. A recent study by Bazzoli found that increasing levels of debt resulted in a greater likelihood of residents choosing specialties other than primary care (29). However, more recent data suggest that selection of a specialty is not related to debt (26). Regardless of this relationship, interest in the primary care fields is declining. A decreasing number of students are pursuing careers in general internal medicine and family practice; the number of graduating students interested in general internal medicine has decreased by 37% since 1981, and the number interested in family practice decreased by 16% from 1987 to 1988 (30, 31).

Have these changes affected those pursuing a medical education? It would be foolhardy to argue they have not. Eisenberg has emphasized the privilege inherent in becoming a physician (32), an emphasis that is certainly warranted. But it is equally true that the practice of medicine is changing, and that these changes have not been viewed favorably by those considering a medical career.

The Residency. During the past several years, for the first time in this century, there are more physicians attempting to enter residency programs than there are places. In 1971, 9,004 physicians applied for 16,550 available positions; in 1987, there were 24,630 physicians for 19,955 places (33).

Although virtually all U.S.-trained physicians are able to find residency positions, competition for residency training in certain specialties has markedly increased. This competition is most notable in surgical specialties, which are believed by many to be producing an excessive number of specialists at the expense of primary care physicians (34). This has intensified the pressures on students considering such fields to make choices early in their careers and to focus their elective periods toward subjects that will improve their chances of obtaining a residency rather than broaden their medical education. All of these changes have contributed to an increasing frustration in those studying medicine, breeding an unhealthy cynicism and anxiety.

Existing market forces may correct the imbalance between primary care and specialty residencies, as may the government's move to decrease funding for residency and, to a greater extent, fellowship training, through cuts in Medicare reimbursement (35). Whether this will exert pressure on students to enter primary care fields, as well as less populated specialties, is doubtful. The number of U.S. graduates matching to general internal medicine programs has decreased each year since 1985. In a recent report, Graettinger notes that the filling of internal medicine programs by U.S. graduates has decreased to 60% of available positions, 21% fewer matching in 1989 than in 1985 (35a). This has been accompanied by an increasing number of positions offered to foreign medical graduates, whose numbers in internal medicine programs have increased by 740 since 1985.

The Academic Physician

Physicians who choose to remain in academic medicine will also be markedly affected by these changes. The ivory tower of academia is not only becoming tarnished, it is sinking under the heavy burden of expanded delivery of unreimbursed health care costs, consistent decreases in funding of the National Institutes of Health in terms of real dollars, the disproportionate effects of the Gramm-Rudman-Hollins cutbacks, and the federal administration's continuing erosion of funding already allocated to health care.

The number of biomedical researchers in the U.S. has been estimated at 90,000, with 18,000 physicians and about 35,000 biomedically trained scientists with PhDs in academic research (36). The decreasing number of applicants to medical school may also be accompanied by a markedly diminishing number of students desiring a career in biomedical science. The decreasing availability of physician-scientists to compete for National Institutes of Health grants has already been demonstrated. In 1970, of the grants awarded to principal investigators, 37% were to MDs, 6% to MD-PhDs, and 51% to PhDs. In 1987, these figures were 26%, 4%, and 64%, respectively. This decrease in grants to MDs is related not to the quality of MD applicants but rather to a decrease in the number of physicians submitting applications, in spite of the fact that the proportion of medical students engaged in research projects increased from 34% of men and 30% of women in 1982, to 47% of men and 42% of women in 1988. Thus those interested in actual research positions or fellowships clearly has decreased (37).

In an attempt to maintain the level of funding for research, private sources of funding have consistently increased, rising from 32% of funding of principal investigators in 1972 to 64% in 1982 (38). Tuition income has also become an increasing proportion of institutional income; however, the marketplace limits the extent to which tuition can substitute for diminishing federal support. Faculty practice plans are under no such limitation. Academic physicians are being pressured each year to expand their clinical activities, at times at the expense of their research endeavors (39). A survey by the Association of American Medical Colleges of 125 medical schools documented this concern. In this survey, one half of faculty members felt a conflict developing between financial incentives for clinical practice and the academic mission (40). This is not to imply that the development of academic group practices are either socially undesirable or inimical to the overall academic goals and educational mission of the institutions. As demonstrated by Cohen et al, some such groups can provide better care than traditional clinics and, at times, at decreased cost (41). When this activity becomes the financial mainstay of an academic institution, however, scholarship must suffer. The academic physician may not be an "endangered species" but, in Darwinian fashion, is becoming less academic (42, 43).

The Physician in Practice

The forces bearing on the practice of medicine not only are of financial concern to the practicing physician but also are raising serious ethical issues that may ultimately exert a greater influence on quality of care. The most relevant changes include (a) diagnostic-related groups (DRGs); (b) new mechanisms for reimbursing physicians for their services; (c) the proliferation of health maintenance organizations (HMOs), euphemistically referred to as "managed medical care"; and (d) increasing liability premiums.

Diagnostic-Related Groups

The creation of Medicare in the 1960s has been exceedingly successful in providing quality health care to the elderly. Since 1968, mortality rates among the elderly have declined to lower levels than in other Western countries, life expectancy at age 65 increasing by almost 2½ years. The majority of elderly people now seek medical care regularly, at least as often as other adults (44–46). These accomplishments, however, have been exceptionally costly and of increasing concern, evoking predictions of the ultimate bankruptcy of the entire Medicare system.

In 1983, in an attempt to restrain increasing costs, Congress enacted the current hospital prospective payment system for Medicare, termed diagnostic-related groups (DRGs). DRGs allow for reimbursement of all hospital care through assignment of one of 467 possible categories to each case, the assumption being that differences in efficiency rather than the characteristics of a patient population or quality of care are the causes for differences in charges (46, 47). With this technique, a fixed payment is made for each case, the amount depending on which DRG has been assigned to the case, with adjustments for community wage levels and direct and indirect educational costs. The payment is dependent on a principal diagnosis, a secondary diagnosis, age, presence of complications, and status on discharge; up to 5% of total payments are used for cases clearly outside DRG reimbursement categories.

Although DRGs have met their objectives in limiting the increasing cost of medical care and providing hospitals with the incentives to improve efficiency, the DRG system has occasioned many problems. DRGs do not routinely consider severity of illness, socioeconomic characteristics of patients, type of institution providing the care, or reimbursement for all costs that may be incurred (48). In addition, they fail to insure homogeneity or specificity of disease being classified, resulting in considerable overlap (49–52). The appearance of AIDS as a major health concern in urban areas and the inadequacy of DRGs to reimburse sufficiently for the complex care needed and being provided add yet additional strains on hospitals, especially those serving primarily indigent populations.

Inappropriate classification, whether intentional (as in DRG creep) or inadvertent, can also result in considerable differences in payment (53). DRG reimbursement not based on actual utilization of services allows for considerable manipulation in an attempt to maximize income, including increasing admissions of nonseriously ill patients (54).

Triage of seriously ill patients to municipal institutions or nursing homes so as to avoid overruns on DRG reimbursement is far from hypothetical. Schiff et al documented a dramatic increase in transfers to Cook County Hospital in Chicago since the onset of DRGs (55). The number of intrahospital transfers rose steadily, from 1,295 in 1980 to 6,769 in 1983. Tellingly, 89% of the patients transferred were black or Hispanic, 87% lacked medical insurance, only 6% had consented to the transfer, and 24% were medically unstable. Of most concern was a mortality rate of more than twice that of patients who were not transferred. Illinois does not stand alone with respect to this problem. In Dallas, the number of transfers increased from 70 per month in 1982 to 200 per month in 1985, with 77% of those transferred lacking medical insurance. Ansell and Schiff have estimated that 250,000 patients in need of emergency medical care are transferred for economic reasons each year (56).

The potential for premature discharge in an attempt to maximize income has been recognized by the Department of Health and Human Services (HHS). HHS has given final approval for a statement to be forwarded to all hospitalized patients containing the process to be followed in contesting hospital-ordered discharge decisions (57,58). This not only will have the intended effect of informing patients of their rights but also will serve to condition consumers that, indeed, this system is not to be trusted.

Mechanisms for Reimbursing Physicians

In-Hospital Services. The success of hospital DRGs periodically raises the issue of physician DRGs for in-hospital services. Unlike hospital DRGs that indirectly affect physician income through early discharge, physician DRGs would require acceptance of assigned reimbursement for inpatient care and markedly affect physician income. Physician DRGs package payment units as a bundle of related services instead of a single procedure. All services performed by physicians during the hospitalization, such as anesthesia, radiology, and other consultations, would be included as a single payment to the primary care physician. This would encourage physicians to cut back on marginally necessary services and consultations, since such costs are taken from the payments given to the primary physician.

There are, however, as described by Mitchell et al, many unanswered questions concerning physician DRGs (59). These include inadequate attention to geographic variation or specialty of physicians, a stimulus to initiate expensive, specialized services outside of the hospital, the potential for DRG creep, and a financial incentive to underserve the patient. Physician DRGs would be a "lottery" with large gains for some and severe losses for others. Although this subject has been exhaustively reviewed and found unworkable, it will not be surprising to see it resurface once again (60).

Assignment of Fees. It must be emphasized that, as with any profession, some physician fees were, and remain, exorbitant. Although physician fees represent a small part of health care costs, physicians serve as gatekeepers to the system and, as such, can markedly influence total costs. In an attempt to contain physician fees over the years, the federal government and other third-party carriers have attempted to encourage physicians to accept a recognized reasonable fee assignment in lieu of their customary fees. Of existing insurance programs, Medicare is currently the largest and, undoubtedly, the most powerful. Medicare's methodology for physician payment has always been referred to as the customary, prevailing, and reasonable (CPR) fee. CPR fees, designed to bring medical care to the elderly, have been quite successful as well as quite costly.

Congress, in 1984, through the Deficit Reduction Act, acted to contain expenses. As part of this act, a participating physician program was established, accompanied by a freeze on CPR charges. Encouragement was given to physicians to become "participants" in Medicare by allowing Medicare-participating physicians to increase their fees in the future and withholding permission for fee increases from nonparticipating physicians. Were Medicare assignments to be made mandatory, refusal to accept assignment would eliminate an important source of income (44, 58).

Massachusetts as a Model. Other third-party carriers have long promoted voluntary participation of physicians in assigned-fee programs. Although many have speculated that mandatory assignment of physician fees would result in adverse consequences to both physicians and patients, until recently, little data existed. However, a model has now emerged from the state of Massachusetts. Although the state is not yet addressing the quality of care provided under mandatory assignment, Massachusetts has instituted mandatory assignment for all physicians. The law on mandatory assignment included a clause allowing insurance companies to charge physicians retroactive premiums based on costs of malpractice settlements years after the initial premiums were collected (61, 62). A universal health insurance act was accepted, to be phased in over a four-year time frame. In an attempt to emphasize the feeling of the state on mandatory assignment, most recently the governor signed a new law, passed by a wide margin in both chambers of the legislature, compelling physicians in the state who treat Medicare patients to accept assignment or lose their licenses to practice medicine (63, 64). Although the objective of universal health care is laudable, the costs of providing such care have probably been underestimated. In Massachusetts the increasing state deficit has resulted in a slowing of this momentum. Implementation of this law is currently under challenge, although it has been initially upheld in federal court (63).

The effects of these changes on physicians are predictable. Faced with fixed reimbursement for all medical services, unaccompanied by adequate cost-of-living increases, and an agreement by the state on retroactive billing for supplemental insurance premiums, physician anger and frustration erupted (65, 62). Although mandatory assignment will undoubtedly reduce the costs for physicians' professional fees, the overall consequences of such policies are not yet known. Nonetheless, several other states are considering instituting mandatory assignment.

Resource-Based Relative-Value Physician Payments. Most recently the existing Medicare physician reimbursement schedule has been reviewed in an attempt to provide more equitable payment for services rendered. This system, developed at Harvard, would increase fees paid to many primary care physicians, while decreasing those paid to some surgical specialists and the more technology-oriented specialists (66). This schedule, which should cover all specialties, would be based on a relative value scale (RVS) consisting of relative physician work and practice costs, a conversion factor to convert the RVS to a payment for each service, and a geographic multiplier to take into account variations by locality. These recommendations are just beginning to be debated by concerned groups of both physicians and providers.

Managed Medical Care

In the 1990s, the catchword for provision of "innovative health care" will be managed medical care. This may be through a variety of mechanisms, including preferred provider organizations (PPOs), health maintenance organizations (HMOs), and independent practice associations (IPAs) (67–69).

However, before looking at these models of "managed medical care," note that this term itself has now ushered in a new industry which neither owns hospitals nor provides health care, but rather sells consultant services to insurers and corporations to help determine the most cost-efficient manner to provide employees with medical benefits (69, 70). Some of the most prominent of these companies are reported to have revenues of up to $200 million a year as part of the for-profit medical marketplace.

Preferred Provider Organizations. PPOs are really less cohesive organizations than groups of health care providers who have developed contractual arrangements with groups in need of health services, fees for such services being discounted from the usual or customary charges (68).

Health Maintenance Organizations. HMOs allow the provision of health care for other than fee-for-service under a prepaid or capitation system of physician payment. In 1984, 7%, or 16 million persons, were enrolled in HMOs, with an increase projected in every successive year to over 30 million enrollees (12, 69, 71). Up to 20%–30% of the population of Los Angeles, San Francisco, Seattle, Portland, and Minneapolis are now members of HMOs, and it was anticipated that by 1990 over 65% of the population would be enrolled. Corporations, which have seen progressive increases in health care costs erode, have become active promoters of such programs (65, 70, 72). A recent survey found that 49% of Fortune "500" companies have encouraged the use of HMOs to contain health benefits costs, and another 27% are considering future promotion of these policies (73). By requiring employees to make salary contributions to health care premiums for fee-for-service policies, corporations are able to "encourage" employees to join HMOs rather than maintain traditional insurance coverage.

The basic objectives of an HMO are to maintain an acceptable quality of care, eliminate financial barriers to care, and decrease the cost of providing services through appropriate rationalization. As might be expected, the concept attracted a number of investors, and for-profit HMOs developed quite rapidly.

For-profit HMOs were estimated to be attracting up to 50% of people joining HMOs, although the availability of not-for-profit HMOs was fourfold greater (74). The potential for profit by management in these plans is considerable. Investors have poured venture capital into these programs, at one time making HMO stocks among the fastest growing on Wall Street. Recognizing the acceptability of HMOs to consumers, commercial insurers and Blue Cross/Blue Shield have developed their own versions of HMOs or have developed relationships with established HMOs. Teaching hospitals, far from immune from this lure, have developed partnerships with HMOs in an attempt to retain appropriate patient populations (75).

Not infrequently, HMOs have offered further discounts to corporations, becoming preferred provider organizations (PPOs). Consistent with our free-market system, this competition has resulted in considerable price cutting. As an example, in Chicago, where the number of HMOs grew from 12 to over 20, more recent competitors have offered premiums of less than $100 per month (76). In California in 1985, HMOs also started to decrease their premiums, and it is believed that further decreases will occur. Although Wall Street has focused interest on the ability to maximize one's investment, the attention given to HMO enrollment has not been accompanied by comparable scrutiny of the demographic range of persons accepted by HMOs or the effects that these programs will have on either the physician or the consumer.

In fact, as noted by Ginzberg, for-profit HMOs have run into considerable difficulty by understating the financial resources needed to develop high-quality, integrated health care facilities (77). The entry of health insurance companies into this domain also added to the risks involved. In fact, in many of these organizations, the capitation level for each physician is such that the provision of other than minimum care may result in considerable financial liability for the physician (78, 79).

The age and socioeconomic status of enrollees are also of importance. If the proportion of enrollees 50 years of age or older exceeds a critical level, the HMO may become nonviable. This possibility has been addressed quite vigorously by management in attempts to restrict the number of elderly or seriously ill persons able to join. Although many HMOs working with IPAs have established quality standards, in some for-profit corporations the bottom line is clearly to make a profit. Monitoring is focused on cost containment rather than quality of care. When the physician is employed in a for-profit enterprise in which financial gain can be made by not providing services, a number of ethical issues arise. These questions have resulted in much disillusionment with health care in such settings (80–83).

Independent Physician Associations. IPAs consist of a loose network of physicians in private practice who negotiate with HMO management to accept a panel of patients under capitation reimbursement for primary care. Through the IPA, physicians see patients in their own offices, do not provide care exclusively to HMO consumers, and derive a net income from the HMO indirectly related to the amount and complexity of services provided. IPAs, by allowing physicians a degree of autonomy not seen in staff HMOs, have become exceedingly popular, increasing by 30% between 1985 and 1986 (84).

For those physicians practicing in IPAs and at the same time maintaining fee-for-service patients, the possibility of establishing a two-tier system of health care becomes quite real, and the line between "luxury" and "quality" health care becomes more difficult to discern. Restrictions by some HMOs of the number of fee-for-service patients physicians may keep in their practices further limit the physician's flexibility in maintaining income while providing quality care.

Specialists participating in HMOs are also under considerable constraints. The fees for services provided are usually less than the fees allowed by Medicare or accepted by other third-party carriers. In some instances, HMOs provide a standard fee regardless of location of practice and despite the wide geographic variations in the cost of living. The specialists are also dependent upon the primary providers of care, who, in turn, will realize an increase in income for every referral not made. Steinwachs et al have demonstrated considerable variability in specialty visits by type of HMO (14).

The Effects of Medical Liability

Malpractice Premiums. It belabors the obvious to state that a crisis point has been reached in medical malpractice, with respect to both premiums charged to physicians and awards made. Although one cannot argue against adequate compensation for wrongful injury, the magnitude of some awards remains questionable. The overall effect, nonetheless, has been unacceptable if not exorbitant malpractice insurance premiums. Although it is claimed that these huge increases are mandatory if insurance companies providing liability coverage are to remain solvent, the evidence suggests otherwise.

As observed by Hunter, between 1976 and 1977, as insurance costs rose by 300% or more for physicians, profits accruing to insurance companies increased by 500% (85). Hunter suggests that in order to attract capital in the early 1980s, these companies began insuring poor risks to obtain as many premium dollars as possible to invest at high interest rates. The ultimate decline in profits fostered exorbitant increases in premiums and a decrease in coverage. Although increasing liability awards are used as justification, in fact, the median award has remained remarkably constant over the past 25 years, the average award increasing because of a few large settlements. The most telling factor, however, as noted by Hunter, is the observation that as the industry raised premiums by $25 billion due to losses, the stocks of insurance liability companies rose by 50%, twice the Dow Jones Industrial average, rising an additional 22% in the first quarter of 1986.

However, it appears that, in response to increasing public, physician, and legislative outrage, premiums may finally be stabilized (85). This stabilizing may reflect an attempt by insurance companies to thwart mandated rates rather than a true trend.

The most recent evidence is somewhat more encouraging. The reasons are as unclear as those associated with the impressive escalation in premiums. In some parts of the country, rates are even decreasing (87a). However, inconsistencies persist. In New York state, where the number of malpractice lawsuits filed has been reported as decreasing from 14,222 in 1986 to 4,297 in 1988, and where the number of cases reaching trial has decreased 40% since 1985, no decreases in premiums were expected, and the anticipated increase was reported in May 1989 as not exceeding 5% (87b).

Many have argued that one factor in the rising cost of medical care is the need to practice defensive medicine, resulting in ordering excessive tests to convince a potential jury that, indeed, every possible technique was used to diagnose disease or to treat an underlying malady. Those who practice litigation will not be insensitive to the merits of a suit in which the malpractice is alleged to be based, in whole or in part, on medical decisions relating to cost of care considerations.

Peer Review and Suits for Damages. Another problem that has plagued physicians' attempts to diminish litigation through restricting activities of peers believed to be less than competent is the fear of legal recourse by those disciplined. This issue, recently debated in Congress, has been resolved by the Health Care Quality Improvement Act of 1986. This legislation, designed to encourage physicians to prevent inappropriate medical care by other physicians, confers immunity to physicians and hospitals participating in the peer-review process. This immunity, preventing the initiation of antitrust suits, has been accompanied by a system for more accurate tracking of adverse incidents (86, 87). Yet individual incidents of physicians successfully defeating peer review and suing for damages continue to occur, and are of increasing concern to participants in the peer review process.

Institutional Liability. The effects of liability on academic institutions, independent of potential malpractice claims brought against faculty in medical services plans, are also considerable. As described by Challoner et al, the increase in risk associated with care provided by students and house staff, even when supervised, makes these institutions especially vulnerable (88), because the expected standard of care and the use of advanced technology are often set at a higher level than that seen in a community setting.

Consumer Acceptance

Consumer reaction to this focus on this aspect of health care costs has been, for the most part, quite favorable. Less is known about the impact of these savings on the quality of care provided, particularly since there are few, if any, hard data or experience on which to draw. There is yet no consensus on how best to obtain these data. For the consumer, only when one develops an illness can the acceptability of HMOs be adequately tested.

It is suggested that, although the insured consumer may currently be pleased with changes in the provision of health care, the quality of care provided may be affected in a number of ways:

- the potential income gain for hospitals by a rapid turnover of patients may result in premature discharge;
- individuals needing hospitalization for serious and costly illnesses may be transferred to municipal hospitals rather than receive care at voluntary or for-profit institutions;
- hospitalized care under research protocols will be markedly diminished;
- physician payments through capitation, far from allowing patients more time to speak to physicians, may result in a "cost efficient" practice translated into as little patient contact as possible;
- profit sharing of IPAs through diminishing laboratory testing and referrals may restrain needed consultative or diagnostic services.

Consumer enthusiasm over savings through decreasing medical costs, however, does seem to be on the wane. It is ironic, yet true, that despite the economics set in place by DRGs, deductibles paid by Medicare recipients continue to increase. As hospital stays continue to shorten, the cost per hospitalized day increases. Since legislation sets Medicare deductibles by cost per day, deductibles will rise despite a decrease in annual hospital costs. Although prospective payments have substantially reduced Medicare's hospital costs, the effect that this system has on providing quality care to the elderly remains to be determined (89).

Enrollment in HMOs in certain areas is diminishing. In Minneapolis/St Paul, a national leader of HMOs in the early 1980s, HMO enrollment among state employees has decreased from 46% to 42%. Those who have dropped out have chosen a combination of prepaid plans and traditional indemnity insurance (90). Maxicare, one of the largest HMOs, is suffering considerable losses, enrollment in various plans decreasing by 50% to 70% (90a). It is suggested that as individuals become ill, or as the graying of the HMO population occurs, more and more dissatisfaction will be expressed by consumers over the quality of care provided by many HMOs. These feelings will probably appear gradually, gaining momentum at a point in time when the financing of health care has become relatively fixed, making change difficult.

In any case, and not surprising, there is little question that the indigent are the losers in this drive to cut costs. Between 1975 and 1983, as the proportion of low-income groups covered by Medicaid decreased from 63% to 46%, and the number of persons without any health insurance increased by 20% between 1979 and 1984 (91), surveys defining the effects of these changes demonstrated that low-income persons received significantly less care if they lived in states without or with limited Medicaid programs. Poor children saw physicians 40% less often and poor rural residents 22% less, suggesting that the ability of hospitals and clinics to provide uncompensated care may be quite limited (80, 81, 92).

The New Ethics of Medical Care

Although one might argue the ultimate effects of these changes on the practice of medicine, the ethical issues facing physicians are becoming increasingly difficult to address. The actual packaging, marketing, and accumulation of revenue in these for-profit systems clearly demonstrate that capitalism is alive and well. At present, approximately one-third of the acute care hospitals are owned, leased, or managed by multihospital systems. It is anticipated that this trend will continue so that by 1990, multihospital systems will control over 50% of the acute care beds in the country (93). The ability of these organizations to generate profits has also been clearly demonstrated. However, their ability to provide cost-effective care, quality care, or equal access to care has been less well documented. Studies of cost-effective areas have demonstrated that expenses incurred are 3%–10% higher in for-profit institutions; however, levels of service are often diminished (94). Profits are accumulating to the entrepreneurs and those heavily vested in venture capital.

It is equally clear, however, that the individual practice of medicine, in which the physician is an independent agent, is rapidly declining. Between 20%–25% of all nonfederal physicians in practice are salaried, and 40% of all physicians and 60% of all female physicians under 35 years of age are also salaried (95). Physicians are inevitably moving into the position either of working for a salary or of being paid by capitation, income being inversely related to the services provided.

As a result the physician, as a businessperson, is faced with a number of ethical issues. As emphasized by Relman, there have always been physician entrepreneurs (95). However, increasing numbers are realizing that, in order to retain a degree of independence, as well as maintain financial stability, they must become more involved in investment and management than in the actual provision of health services. As a result, practicing physicians have now obtained financial interests in laboratories, imaging centers, walk-in clinics, health maintenance organizations, dialysis units, and ambulatory surgical care centers. All of these facilities are able to exist and to thrive only through physician referrals. The effects that this may have on practice patterns are far from hypothetical. A recent report by the Inspector General found that physicians with financial interests in laboratories referred approximately 45% more services for Medicare patients than other physicians (96). In addition to this limited-partnership arrangement in a specific facility, physicians are also active participants in venture capital companies; up to 25% are estimated to be involved in such activities, achieving profits on investments of up to 100% (97, 97a, 97b).

Examples of conflicts of interest in this area abound. Whether they involve cardiologists sharing in profits or accepting gratuities from companies producing pacemakers, or ophthalmologists accepting similar inducements from manufacturers of intraocular lens implants, or for-profit hospital chains sharing profits from reimbursement with physicians who use their services, or physicians receiving a percentage of profits when a "DRG patient" is treated for less money than his or her hospital receives from Medicare, or the advertising of surgical procedures by minimizing risks and magnifying gains, the ethical issues are compelling (98–100). However, even more subtle forces exist when financial incentives are used primarily to decrease the costs of medical care (101). Consider the leverage exerted by an HMO in the affairs and operation of a particular hospital to which its clients are preferentially referred. Physicians not enrolled in an HMO, and who do not have admitting privileges at the particular hospital, were not likely to be asked to care for the patients.

These issues are now being debated by many medical societies as well as by public interest groups. In an attempt to maintain control, medical societies have either established, or are in the process of establishing, their own IPAs. However, developing appropriate ethical standards is far from easy. As noted by Costilo, the Federal Trade Commission might well review as unduly restrictive a statement of ethical behavior that would limit activities which, in the normal marketplace, not only are considered appropriate but are encouraged (102).

Regardless of the position of the profession, however, as widely outlined by Hyman and Williams, the government has proceeded to define boundaries. Final regulations under the Medicare and Medicaid Patient and Program Protection Act, which will be issued shortly, will considerably restrict a physician's ability to invest in health care facilities and make many existing referral patterns illegal. Even more restrictive is a bill, the Ethics in Patient Referrals Act (HR 939), introduced by Representative Stark, which would prohibit payment to any physician who holds an interest in a laboratory to which he or she makes a referral.

The ethical issues with respect to the physician as a fee-for-service practitioner and a hospital attending are also of concern. The establishment of DRGs has placed pressure on physicians to discharge their patients as early as possible as well as to perform fewer diagnostic services while the patient is hospitalized. The attempt to maximize hospital income through DRG creep is aided and abetted by the actual overlapping of DRGs. The pressures can only be intensified when, in fact, physicians are direct recipients in the sharing of savings by the hospital.

Mandatory assignment, unaffected by continued cost-of-living increases in managing a practice and soaring malpractice premiums, leaves the physician little option with respect to devoting less attention to activities that are either time consuming or not cost effective, such as speaking with patients, or are associated with a greater risk of medical liability, such as treating acute trauma or providing "high-risk" obstetric care. Individual physicians committed to primary care are beginning to question their commitment and their ability to survive in this new environment. The potential loss of the services of these physicians could markedly effect the quality of medical care received in many areas of the country (103, 104).

The Future of Cost-Efficient Health Care

Uppermost in the public's mind, at this time, is the unacceptable level of cost of medical care. As noted by Ginzberg, the consequent changes have resulted in a marked destabilization of the basic foundations of medical care: (a) the nonprofit community hospital; (b) the physician as an independent practitioner; and (c) the cross-subsidization of care, allowing providers to care for the indigent (77).

It is not difficult to predict that, despite these changes, the cost of medical care will continue to increase. As an example, although Medicare has been quite successful in co-sharing physician fees for individuals, the volume of physician services to Medicare beneficiaries increased 100% between 1975 and 1985 (105). As increasing curbs are placed on expenditures, both the quality and the range of services offered must start to be affected. Two states, California and Oregon, have already begun to prioritize care that will be "reimbursable." The effects of these decisions remain to be seen. Certainly, decisions concerning high-cost procedures, such as transplantation, and the use of expensive diagnostic techniques will be increasingly made in conjunction with financial considerations rather than solely by practicing and attending physicians on the basis of medical indications.

The practice of medicine assuredly will continue in the face of the inevitable and perhaps unending debates. The upward trend in physicians' income may be slowed, even levelled, but it will probably not plummet. The public, however will eventually realize "for whom the bell tolls." Whether in this decade before the third millennium, and whether the bell will be heard before a decrease in quality of health care is appreciated, remain to be seen. Perhaps, as predicted by Fuchs (106), a counterrevolution in health care financing will ultimately occur.

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Opportunistic Infections of the Testis In the Acquired Immunodeficiency Syndrome

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Abstract

The testes of an autopsy sample of 56 patients with acquired immunodeficiency syndrome (AIDS) and systemic opportunistic infections were studied for the presence and type of testicular infection. Light-microscopic evidence of opportunistic organisms (cytomegalovirus, *Mycobacterium avium-intracellulare,* and *Toxoplasma*) was present in 22 cases (39%). Based on the prevalence and histologic features of the testicular infections and the biological characteristics of the specific organisms, the possible sexual transmission of opportunistic organisms in AIDS is discussed.

PATIENTS with the acquired immunodeficiency syndrome (AIDS) are susceptible to a wide array of opportunistic infections, including viruses, protozoa, mycobacteria, and fungi (1). The significance of these opportunistic infections is well recognized since they constitute the immediate cause of death in almost all AIDS patients (2, 3). The role of sexual intercourse in the transmission of opportunistic infections in AIDS has not been thoroughly investigated. This can in part be explained by the fact that cytomegalovirus (CMV) (3, 4), *Mycobacterium avium-intracellulare* (MAI) (3, 5), *Toxoplasma* (Toxo) (3, 6), and most other AIDS-associated opportunistic organisms are ubiquitous agents, present in the environment to which all patients are likely to be exposed. Thus, the manifesting infectious processes predominantly reflect the underlying immune suppression rather than a unique environmental exposure (3). Unique situations which result in an unusually heavy exposure to infectious agents, however, might predispose certain AIDS subgroups to specific infections (3). It can, therefore, be postulated that homosexual AIDS patients are particularly vulnerable to opportunistic agents that are sexually transmittable.

To the best of our knowledge, only the human immunodeficiency virus (HIV) (7, 8) and CMV (9) have been reported in semen analyses of AIDS patients or HIV-positive homosexual men. The high prevalence of CMV in the semen of homosexual AIDS patients is not unexpected in view of the frequent presence of this organism in the semen of homosexual men even in the pre-AIDS era (10, 11).

We studied the prevalence of testicular infection in an autopsy sample of 56 AIDS patients who had died with opportunistic infections and analyzed the histopathologic features of the involved testes with special reference to the exact location of the organisms within the testis.

Materials and Methods

Between 1984 and 1988, 69 male patients who fulfilled the Center for Disease Control crite-

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ria for AIDS were autopsied at St. Vincent's Hospital and Medical Center, New York. Of these, 56 had evidence of opportunistic infections at autopsy. The present study is limited to this sample of 56 patients. Fifty-one of these cases were included in our previous study on testicular atrophy in AIDS (12).

The hospital charts were reviewed for age, AIDS risk factors, and history of classical venereal diseases. The autopsy protocols were reviewed for the cause of death and major necropsy findings. The histologic sections of the testes (one in 17 cases and two in 39 cases) were routinely processed and stained with hematoxylin-eosin as well as Ziehl-Neelsen preparation for acid-fast bacilli.

Results

Clinical Findings. The age of the patients ranged from 22 to 69 years (mean 39.7 years). Fifty-four patients (96%) were homosexual, one of whom had a history of intravenous drug abuse, and two patients were heterosexual drug addicts. Venereal diseases were reported by 39 of 40 patients (98%) who were specifically questioned (gonorrhea and syphilis in 22 cases, gonorrhea only in 12 cases, and syphilis only in 5 cases). In all cases death was attributed to overwhelming opportunistic infections, associated with Kaposi's sarcoma in 18 cases and with malignant lymphoma in 5 cases.

Pathologic Findings. Extratesticular opportunistic infections diagnosed at autopsy included disseminated CMV infection in 34 cases, MAI in 25 cases, and Toxo in 10 cases. Twenty-five patients died with *Pneumocystis carinii* pneumonia. Fungal infections were less common and consisted of cryptococcosis (4 cases), candidiasis (2 cases), and aspergillosis (2 cases). (See Table.)

Opportunistic testicular infection was demonstrated in 22 cases (39%). Cytoplasmic and intranuclear inclusions consistent with CMV were identified in 9 cases (16%), accounting for testicular involvement in 26% (9 of 34) of the cases with systemic CMV infection. The viral inclusions were identified within the lumen of the seminiferous tubules in 6 cases (Fig. 1). The interstitial stromal cells contained inclusions in 8 cases and the endothelial cells contained inclusions in 4 cases.

Acid-fast organisms clustered in globi, consistent with MAI, were present in eight cases (14%), suggesting testicular infection in 32% (8 of 25) of the cases with systemic MAI. The infection was evidenced as single or grouped histiocytes with a pale grayish granular or finely fibrillary cytoplasm. These histiocytes were confined to the interstitial stroma in 7 cases, often with perivascular clustering (Fig. 2). In one case, small numbers of acid-fast organisms were identified within the seminiferous tubules, in a predominantly basal location. In one instance poorly formed granulomas with central necrosis were present, but in none of the other cases was the infection associated with a significant inflammatory response. The Ziehl-Neelsen stain revealed globi of acid-fast bacteria in all cases (Fig. 3).

Cysts filled with numerous curved organisms, compatible with the bradyzoit-filled cysts of Toxo, were identified in 6 cases (11%), including one of combined infection with CMV and Toxo; this accounted for testicular infection in 60% (6 of 10) of the cases with systemic Toxo. The cysts were located within the tubular lumen in 3 cases (Fig. 4), and in the interstitium in the remaining 3 cases. There was no significant inflammatory response. In 4 cases of testicular Toxo the brain was the only other organ involved, while in 2 cases the infection was generalized, involving brain, heart, and gastrointestinal tract.

Unfortunately, none of the testes were cultured, precluding accurate speciation of the organisms. In all cases, the organisms suggested by light-microscopic examination of the testis were demonstrated in other organs by either culture or immunohistochemistry, or both, allowing a more reliable presumptive identification of their nature in the testis. Semen analyses were not performed.

Discussion

We studied the histologic features of the testes in an autopsy sample of 56 AIDS patients who had died with systemic opportunistic infections. There was a high incidence of 39.1% of the testicular infection in these patients. Chabon et al (13) described testicular infections in 25% of 28 AIDS patients with opportunistic infections. On the other hand, Rogers and Klatt (14) found only 4 cases of opportunistic testicular infections out of 100 AIDS autopsies and Yoshikawa et al (15) did not find any among 31 autopsied AIDS patients.

In our series, CMV was the most frequent testicular infectious agent observed; 16% of all cases showed cytomegalic inclusions, accounting for testicular involvement in 25% of the cases with systemic CMV infection. CMV infection of the testis in AIDS patients has been described by others (13, 14, 16, 17).

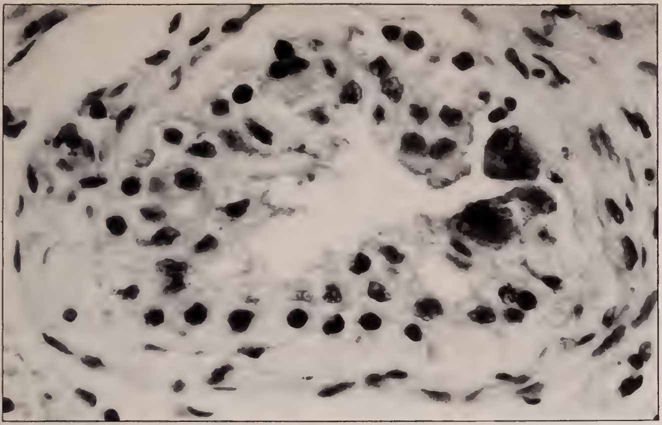

Fig. 1. Two cells lining seminiferous tubule showing characteristic cytomegalovirus inclusions (left); (H & E, original magnification ×350).

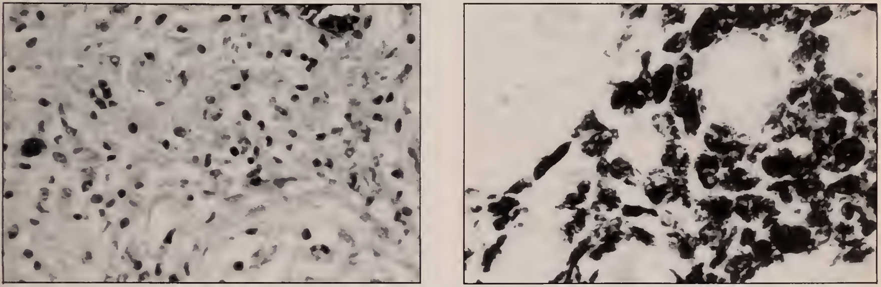

Fig. 2. Left Multiple foamy macrophages laden with *Mycobacterium avium intracellular* seen in testicular interstitium (H & E, original magnification ×100). Fig. 3. Right Acid-fast bacilli stain demonstrates multiple bacilli (dark) within interstitial macrophages (Ziehl-Neelsen, original magnification ×100).

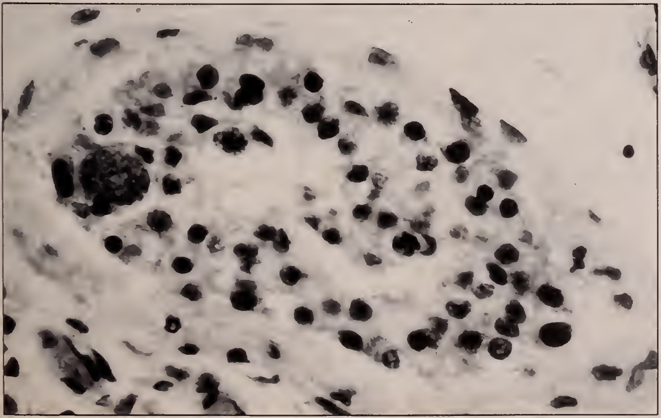

Fig. 4. *Toxoplasma* cyst within tubular lining (left); (H & E, original magnification ×400).

TABLE

Systemic and Testicular Infections in 56 AIDS Patients

Organism	Systemic infection No. of patients	Testis infection No. of patients
Cytomegalovirus	34	9*
Mycobacterium avium intracelluare	25	8
Toxoplasma	10	6*
Pneumocystis carinii	25	0
Cryptococcus	4	0
Candida	2	0
Aspergillus	2	0

* There was one case of combined infection with *Toxoplasma* and cytomegalovirus.

MAI was identified in 14% of all cases, or 32% of the cases with systemic MAI infection. This is in sharp contrast to the findings of others, who did not describe this organism in their studies (13, 14). This discrepancy in results can in part be explained by the fact that we routinely stained all sections with Ziehl-Neelsen. Often the MAI-laden histiocytes in our series were scanty and inconspicuous on hematoxylin-eosin stained sections.

Testicular Toxo was present in an unexpectedly high percentage of cases: 6 of 10 cases with extratesticular Toxo diagnosed at autopsy showed Toxo cysts in the testis. Interestingly, in 4 patients the only organ involved at autopsy was the brain. In the previously reported cases of testicular Toxo in AIDS patients (13, 14, 18), this infection manifested as a necrotizing process involving most of the testicular parenchyma, whereas in our cases the infection was not associated with a significant tissue reaction. A combined infection of CMV and Toxo as observed in this study has been previously described in AIDS patients (13) and in otherwise immunocompromised patients (19). None of the testes in our series showed evidence of a fungal infection, although systemic fungal disease was demonstrated in 8 patients. Isolated cases of testicular histoplasmosis (14) and candidiasis (17) have been reported in AIDS patients. In our series, CMV and Toxo were seen in the seminiferous tubules in 67% and 50% of the cases respectively, whereas MAI was seen predominantly in the interstitium.

Venereal transmission is a known mode of CMV acquisition (4); this virus has been isolated from the urine and semen of homosexual men in the AIDS and pre-AIDS era (9–11). This correlates well with the high frequency of CMV and its intratubular location in this series.

It is generally thought that toxoplasmosis occuring in AIDS and other immunocompromised patients is usually the result of reactivation of a latent infection (6, 20). Less commonly it constitutes a primary infection (6, 20), usually caused by the ingestion of meat containing cysts (6, 20). Rarely, primary infections might result from transplacental exposure, transfusion of blood and blood products, organ transplantation, and laboratory accidents (6). We postulate that in addition to these modes of transmission, Toxo could be acquired through sexual intercourse. Indeed, 60% of the cases with Toxo infection at autopsy in our series had involvement of the testis. Furthermore, in half of the cases the organisms were identified in the lumen of the seminiferous tubules, similar to most of the cases of CMV, an organism known to have a venereal mode of transmission (4). Finally, the organism was present in the form of bradyzoit-filled cysts, an important stage in the *Toxoplasma* life cycle because of its resistance to environmental conditions.

Although the general opinion has been that the transmission of nontuberculous mycobacteria from person to person does not occur (5), a venereal transmission as a mode of acquisition of MAI has been suggested in homosexual patients with AIDS (21). In the testes, we found MAI located predominantly in the interstitium and, therefore, one tends to conclude that testes have no significant role in the transmission of this organism.

In conclusion, we found a high prevalence of testicular opportunistic infections—CMV, Toxo, and MAI—in AIDS patients. Based on the high frequency and specific histologic features of these infections, as well as the biological characteristics of the organisms involved, we postulate that semen might be a vehicle for the transmission of CMV, Toxo, and possibly other AIDS-associated opportunistic infections. Microbiological semen analysis as well as epidemiologic studies are needed to establish the validity of this hypothesis.

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Deterioration of Trapeziometacarpal Arthritis due to Trigger Thumb:

A Biomechanical Evaluation

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Abstract

Patients with trigger thumb and trapeziometacarpal joint arthritis accompanied by swan-neck deformity of their first rays find that their arthritic pain becomes worse whenever their thumbs "catch." Six hands with adduction contracture and arthritis of the trapeziometacarpal joint are studied biomechanically and demonstrate significantly excessive shear forces ($p < 0.01$) around their trapeziometacarpal joint relative to six normal hands. Increased pain with deformity suggests aggressive treatment of trigger thumb in cases such as these.

Stenosing tenosynovitis of the sheath and tendon of the flexor pollicis longus is found in children and adults. The interphalangeal joint flexion deformity, the finding of a subcutaneous nodule of the first metacarpophalangeal joint, and the characteristic snap accompanied by pain while extending the thumb are well known (1–8). Infants and women in the middle decades suffer more commonly from this deformity, although all ages may be affected (3, 7). Trigger thumb has been most commonly associated with DeQuervain's disease, trigger finger, carpal tunnel syndrome, and rheumatoid arthritis, as well as trapeziometacarpal arthritis (2, 3, 5, 6, 9–12).

Arthritis at the basal joint of the thumb often leads to instability (11, 13–17). Adduction contracture of the first web space and compensatory swan-neck deformity of the first ray may complicate painful trapeziometacarpal arthritis (17). The purpose of this study reported here was to demonstrate the biomechanical basis for trigger thumb exacerbating painful arthritis of the first carpometacarpal joint.

Materials and Methods

Two women, ages 57 and 70, without prior history of trauma or rheumatoid arthritis, stated that triggering of their thumbs increased their pain at the basal joint of the dominant thumb. Both patients had trapeziometacarpal arthritis, adduction contractures, and swan-neck deformity of the first ray. These two women are patient 5 and patient 6 on Table 1. Two other patients' hands (four additional hands) with trapeziometacarpal arthritis, adduction contracture, and swan-neck deformity, but no trigger thumb, were also studied, to permit the establishment of a biomechanical trend common to adduction contracture and swan-neck deformity and to the development of deforming forces at the base of the thumb. Six normal thumbs were used as controls.

A Chatillon spring gauge with original, homemade modifications to measure a large range of forces and to accommodate our patients' deformed hands in their position of function was employed (Fig. 1). The test subjects were instructed to extend their thumbs as fully and forcibly as possible. The externally applied force necessary to relax the extensor pollicis longus was then determined. This was accomplished by palpating the extensor pollicis longus at the ulnar margin of the anatomic "snuff box" and

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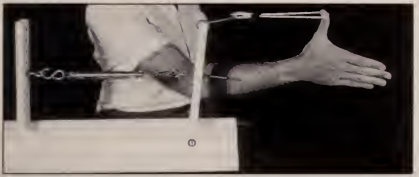


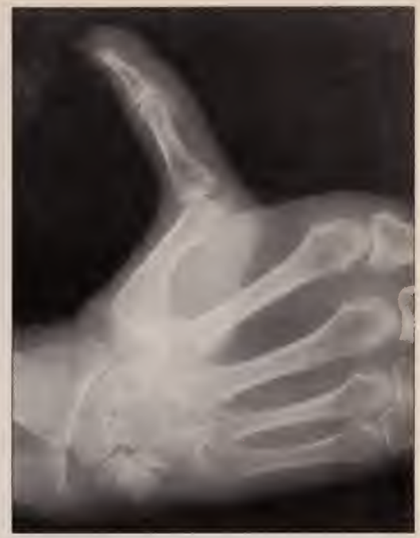


Fig. 1. **Left** Original homemade experimental apparatus with normal hand loaded to a reading of force read at apparatus, F′, of 6 lb on spring gauge. Actual force, F, applied to distal phalanx of E thumb is calculated by moment balance about pivot point of support at right. Fig. 2. **Right** X-ray of patient with adduction contracture, swan-neck deformity, and trapeziometacarpal arthritis under applied load of 9 lb. Direction of applied load is determined by image of line attached to thumb on film.

noting the spring gauge force necessary to relax this tendon. The force was recorded in each subject in their position of function and labelled F′ (Table 1). This was repeated 4 times and x-rays were taken at the average value of F′ in the plane defined by the extensor pollicis longus and the loading force. Typical results are shown in Fig. 2.

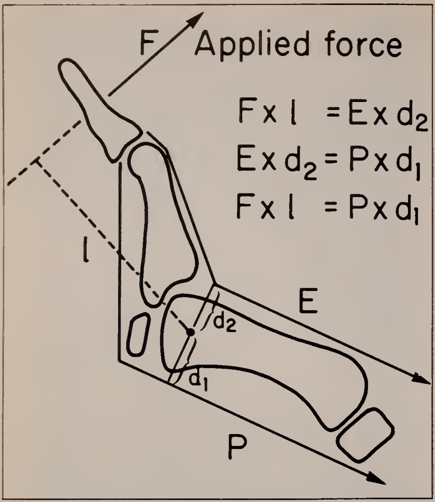
Geometric measurements from tracings of the x-rays were used in all calculations. Using a moment balance about the center of rotation of the test rig, the actual force applied to the distal phalanx, F, was determined (7, 8, 17). Through a free body diagram and moment equilibrium about the first metacarpophalangeal joints, the shear force, S, between the first metacarpal and the trapezium was calculated (Figs. 3, 4). For each hand in the study, the maximum shear force developed in the dorsal direction would necessarily occur when the individual exerted maximum extensor force. This would correlate to the extensor force generated momentarily by the patient with trigger thumb and trapeziometacarpal arthritis as they attempted to move their flexor tendon nodule past the A_1 pulley.

Results

Although the force, F′, applied at full extension for the patients with deformity is only 1.23 times that for the normals ($p < 0.025$), the calculated shear force for the patients with deformity is 3.29 times that for the normals ($p < 0.01$) (Table 2). This large difference at a high level of significance is due to the difference in the geometry between the stressed thumbs of the controls (76.8°) and the patients (58.1°). This angle is created by the intersection of the P vector with its shear S vectorial component whose direction is parallel to the trapeziometacarpal joint space (Fig. 4). Although not significant, the difference in the average tendon forces P developed between the patients and the controls was substantial.

Discussion

Degenerative and rheumatoid arthritis produce a painful and crippling deformity when they affect the trapeziometacarpal joint (14, 16, 18–24). Periarticular soft tissue contractures may also lead to disabling arthritis of this joint (15, 25). As the dorsoradial facet of the trapezium


F
Applied force
$F \times l = E \times d_2$
$E \times d_2 = P \times d_1$
$F \times l = P \times d_1$
l
E
d_2
d_1
P

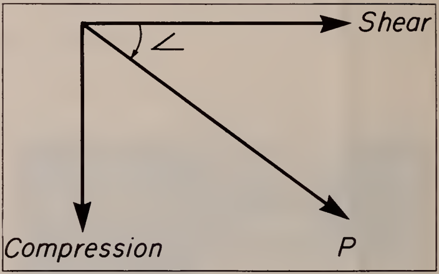


Fig. 3. Left Typical tracing of x-ray of thumb under applied force showing tendon positions, lever arms, and moment of balance. F, applied force; E, force of extensor pollicis longus; P, force of flexor pollicis longus; l, perpendicular distance from applied force to center of joint rotation; d_1, distance from flexor tendon to joint center of rotation; d_2, distance from extensor tendon to joint center of rotation.

Fig. 4. Right Vectodigram showing method of calculating shear force from the tendon force. Direction of tendon vectors was taken from tracing in Fig. 3. Compression, forces perpendicular to trapezium; ∠, angle between p and shear.

erodes under the resulant force from the abductor pollicis longus and the flexor pollicis longus, subluxation exacerbates pain-inhibited loss of motion (23). The head of the first metacarpal collapses in the direction of the contracting adductor, while the proximal phalanx externally rotates (17). Metacarpophalangeal joint hyperextension follows repeated attempts by the patient to abduct and extend the thumb by using all possible extrinsic forces to counteract the adduction contracture. Depressing the metacarpal head serves to further sublux and alter the angle of the trapeziometacarpal joint surface.

Patients with trigger thumb and trapeziometacarpal joint arthritis have their trapeziometacarpal joints temporarily tethered when their flexors catch in their sheaths. Forces which

TABLE 1

Mechanical and X-ray Data from Patients and Normals

	S (lb)	F (lb)	F′ (lb)	l (mm)	d_1 (mm)	P (lb)	∠ (deg)
Patient No.							
1	11.9	4.1	7.5	42	8	21.5	56.5
2	21.7	4.4	8.0	48	6	34.9	51.5
3	4.8	4.4	8.0	13	7	8.1	53.5
4	9.6	4.1	7.5	21	5	17.2	56
5*	8.6	4.4	8.0	45	8	24.5	69.5
6*	18.5	4.9	9.0	47	6	38.5	61.5
Normals							
7	3.7	3.8	7.0	55	13	16.2	76.9
8	3.6	3.0	5.5	55	20	16.5	77
9	2.2	2.7	5.0	49	12	11.2	78.9
10	4.0	3.8	7.0	56	13	16.5	76
11	4.6	4.4	8.0	53	11	21.0	77.5
12	4.8	3.6	6.5	47	9	18.5	79.1

S, shear; F, applied force; F′, force read at apparatus; l, perpendicular distance from F to center of joint rotation; d_1, distance from flexor tendon to center of joint rotation; P, flexor tendon force; ∠, angle between P and S.

* Denotes patients with trigger thumb.

TABLE 2

Results of Comparison of Groups by Student's t-test

	Normals	Patients	Measure
S (lb)	3.8 ± 0.9	12.5 ± 6.4	$t = 3.30$ $p < 0.01$
F (lb)	3.6 ± 0.6	4.4 ± 0.3	$t = 2.72$ $p \leq 0.025$
P (lb)	16.7 ± 3.2	24.1 ± 11.3	$t = 1.42$ $0.05 < p < 0.1$
∠ (deg)	76.8 ± 1.2	58.1 ± 6.5	$t = 6.93$ $p < 0.001$

under normal conditions approximately parallel the first ray are most acutely angulated towards the trapeziometacarpal joint surface under these pathological conditions. They create a vectorial shear component between the first metacarpal and the trapezium which is 229% greater than normal. Patients with stenosing tenosynovitis of the thumb and trapeziometacarpal joint arthritis accompanied by swan-neck deformity of the first ray indicate that their arthritic pain is worse when their thumbs are "catching." The biomechanical basis for the exacerbation of their subluxation and arthritic pain suggests vigorous treatment of trigger thumb in cases such as these. A steroid injection into the flexor tendon sheath and splinting of the first ray in a maximally corrected alignment has stopped or slowed deterioration of trapeziometacarpal arthritis in our patients.

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Synchronous Adenocarcinomas of Jejunum and Cecum Following Transverse Colon Carcinoma

A Case Study

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AND MELANIE J. CASTELLI, M.D.

Abstract

A case of synchronous primary adenocarcinomas of the small and large bowel in a patient previously treated by transverse colectomy for cancerous polyps is presented. These new primaries were incidental findings during surgery for suspected recurrence of colonic carcinoma. Primary tumors of the small bowel are rare, and the diagnosis of primary adenocarcinoma of small bowel in the presence of primary adenocarcinoma of large bowel requires a high degree of suspicion and may well modify the prognostic outcome if detected early.

PRIMARY neoplasms of the small intestine are rare, and malignant tumors of the small bowel account for less than 1% of all intestinal malignancies, despite the fact that small bowel represents 75% of the length and over 90% of the mucosal surface of the intestinal tract (1, 2). Because of their rarity, nonspecific symptoms, and diagnostic difficulty, small bowel tumors are often diagnosed and treated late in their course. The diagnostic difficulty is increased when these tumors arise in association with primary tumors of the colon. A second primary tumor in the small bowel can clinically mimic recurrence of colorectal carcinoma and hence requires a high degree of suspicion that primary small bowel cancers can occur and necessitates extensive sampling for accurate diagnosis.

Case Report

The patient is a 53-year old healthy white man, with no significant family history, who underwent transverse colectomy in 1984 for adenocarcinoma of the colon. The colectomy specimen, measuring 15 cm in length, contained four polyps, one with adenocarcinoma in situ and others showing no dysplasia with negative lymph nodes. A routine follow-up colonoscopy and biopsy in September 1986 revealed adenocarcinoma involving the ascending colon. At surgery, a partially obstructing tumorous growth in the mid jejunum was found, in addition to tumor of the ascending colon. Subtotal colectomy and partial resection of small bowel were done.

Gross Pathologic Findings. The subtotal colectomy specimen, 75 cm in length, contained a raised, ulcerated, firm tan lesion measuring 2.5 × 2 × 0.3 cm, one cm from the ileocecal junction. About 24 cm from the cecum, previous anastomotic site was identified which was grossly unremarkable.

In the resected small bowel, which measured 11 cm in length, there was a raised, firm, irregular lesion in the mucosa measuring 5 × 2.8 × 0.3 cm.

Microscopic Findings. Sections of the subtotal colectomy specimen showed a moderately differentiated adenocarcinoma (Grade II) infiltrat-

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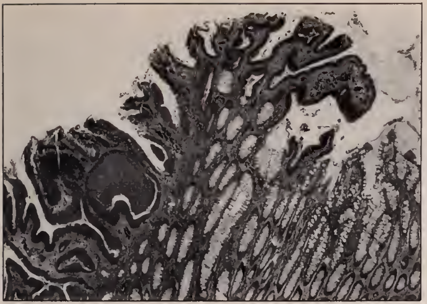

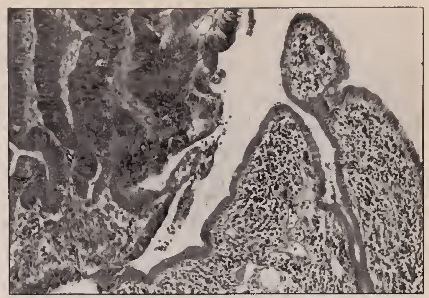

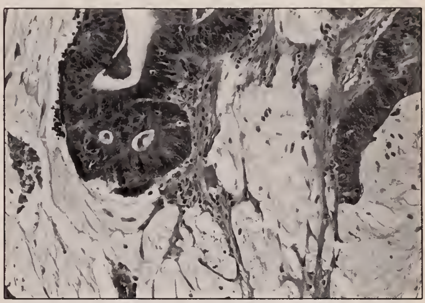

Fig. 1. Left Adenocarcinoma of colon, moderately well differentiated (H&E, original magnification ×25). **Fig. 2. Upper right** Adenocarcinoma of jejunum, moderately well differentiated (H&E, original magnification ×100).
Fig. 3. Right Adenocarcinoma of jejunum. Abundant mucin production (H&E, original magnification ×100).

ing into the muscularis propria (modified Dukes' B_2) (Fig. 1). A transition zone from normal to neoplastic glands was present. Eighteen regional lymph nodes were free of tumor. No tumor was seen on sections from the previous anastomotic site.

Sections of the small bowel showed a mucinous, infiltrating, moderately differentiated adenocarcinoma arising in the small bowel mucosa. An area of transition from normal to atypical to malignant glandular epithelium was seen. The tumor infiltrated the muscularis propria and extended to the serosa surface. Histologically, this tumor was different from that seen in the large bowel, showing abundant mucin production with formation of mucinous lakes (Figs. 2, 3).

Discussion

An unusual case of synchronous small and large bowel adenocarcinoma in a patient previously treated for adenocarcinoma of the colon is described.

The rarity of the small bowel tumors and their nonspecific symptomatology render their preoperative diagnosis difficult. The liquid contents of the small bowel, low bacterial counts, short transit time, alkaline pH, and high concentration of immunoglobulin IgA are some of the factors which might account for the low incidence of small bowel tumors (3–15). They are also difficult to diagnose radiologically and are often missed (6).

The distribution of primary adenocarcinoma within the small intestine varies in different studies, primarily depending on inclusion or exclusion of carcinoma of the ampulla of Vater. Bridge and Perzin (7), in their study of 43 cases of primary adenocarcinomas of small intestine excluding duodenal carcinomas, described 32 cases involving the jejunum and 11 cases involving the ileum. Gupta and Gupta (8) from Varanasi, India studied 58 cases of primary small bowel tumors, periampullary and mesenteric tumors excluded, and found that the ileum was the most common site for benign as well as malignant tumors, followed by the jejunum. However, most other studies show that the distribution of these tumors is highest proximally, with decreasing frequency in the more distal segments of small bowel. Results of 1050 case reports collected by Reiner in 1976 show the same kind of decreasing aboral gradient: 40% duodenal; 38% jejunal; and 22% ileal (9).

Adenocarcinoma is the most common type of small bowel cancer, constituting 32%–54% of all malignant enteric tumors, or 41%–70% if carcinoids are excluded (10–12). Morgan and Busuttil reviewed 18 cases of adenocarcinoma of small intestine and described one patient with a previous history of recurrent polypoid carcinoma of the colon who later developed a mucinous infiltrating variety of adenocarcinoma of small intestine, similar to the case described in this report (13). These tumors arise from the mucosa and generally form a napkin-ring lesion (14).

Small bowel cancers associated with other diseases and malignancies have been reported. Williamson and co-workers studied 171 patients with malignant small bowel tumors that included two cases of adenocarcinoma arising at the site of long-standing Crohn's enteritis, two jejunal cancers associated with celiac disease, two duodenal carcinomas arising in villous adenomas, and one jejunal lymphoma following exposure to irradiation. Multiple primary malignancies were found in 20%–25% of enteric cancers (15). Ouriel and Adams reviewed a series of 65 patients with adenocarcinoma of the small intestine and found that associated malignancies were present in 16 patients (25%), the malignancy being colonic adenocarcinoma in 12 patients (16).

There is a high frequency of secondary synchronous and metachronous neoplasms associated with small intestinal carcinoma (17). However, they are often misdiagnosed as metastatic or recurrent colonic carcinoma when present in association with a colorectal carcinoma.

The prognosis of primary jejunal and ileal carcinomas correlates better with depth of invasion, tumor size, and lymph node metastasis than with histologic grade and gross appearance. Seventy-one percent of patients survive for five years when tumor is confined to the wall of the bowel, 44% if it penetrates through the thickness of the wall, and 14% when lymph nodes are involved (18). Intra-abdominal recurrence of colorectal cancer has a poor prognosis, with an average survival of 11 months and a possible 8% cure rate with further resection (19), as opposed to a five-year survival rate of 13%–41% (20) for primary small bowel adenocarcinoma. Hence, in view of the significant difference in the overall prognosis, a special effort has to be made to identify and diagnose small bowel adenocarcinomas.

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Bleeding Duodenal Leiomyoma

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Case Report. A 70-year-old white woman came to the hospital with gastrointestinal bleeding. Significant in her medical history were a hysterectomy, a cholecystectomy, and an appendectomy.

Five months prior to admission she was admitted to another institution with a hemoglobin of 4.0 g/dL. Supposedly nothing significant was found at that time and she was discharged after being transfused. One month prior to admission her private physician noted her hematocrit level to be 39%. Two weeks prior to admission, the patient noticed increasing weakness, fatigue, dyspnea on exertion, and dizziness. She also noticed palpitations and bloody stools. On the day of admission, she was seen by her private physician and found to be orthostatic; hematocrit was 29%.

Examination revealed no abdominal masses. Rectal examination revealed guaiac-positive stool, but an aspirate from a nasogastric tube was guaiac negative.

Endoscopic study revealed a submucosal mass in the proximal jejunum, which was actively bleeding. It was felt that this mass was probably a lipoma. Celiac and superior mesenteric artery angiogram was then performed via a right femoral artery catheter. The angiogram (Fig. 1) showed an area of diffuse vascular "blush" in the region of the head of the pancreas that was fed by the gastroduodenal artery.

An abdominal computed-tomography (CT) scan (Fig. 2) showed a homogeneous, solid mass in the region of the head of the pancreas intrinsically involving the medial duodenal wall. Furthermore, an upper gastrointestinal series (Fig. 3) showed a smooth extrinsic compression of the medial aspect of the duodenal sweep. No ulcerations were demonstrated. The papilla appeared large and protruded into the lumen of the duodenum (Fig. 4). The contour of the papilla was exquisitely smooth.

In view of these findings, it was felt that the lesion was most likely in the head of the pancreas, although leiomyoma was strongly considered in the differential diagnosis.

One week after admission, the patient underwent an antral-sparing Whipple procedure. Within the duodenal sweep and impinging on the pancreas was a mass of approximately 4 cm, which was redder than normal pancreas. On frozen section it was revealed to be a smooth-muscle tumor. Through a duodenostomy it was seen that this mass abutted the papilla, but there was no intrinsic tumor involving the papilla.

The surgical specimen consisted of a 6 × 4 cm, well-circumscribed mass lying against the serosal surface of the proximal duodenum. The inside of the mass was pink-tan, with multiple hemorrhagic zones. Histologic study revealed the mass to be a smooth muscle tumor without mitoses and therefore a duodenal leiomyoma.

Discussion. Small-bowel tumors make up only 1.5% of all gastrointestinal tumors (1). According to one study, approximately 31% of benign small-bowel tumors are leiomyomas; adenomas make up approximately 22% and lipomas 15% (2). Leiomyomas are found at all levels of the small intestine, but occur most often in the jejunum.

The most common initial symptom of duodenal leiomyomas is bleeding, which results in either chronic anemia or melena (3). Bleeding is secondary to central necrosis and ulceration of the overlying mucosal surface (4). According to some reports, hemorrhage occurs in 40% of cases (5, 6).

These lesions are often difficult to diagnose.

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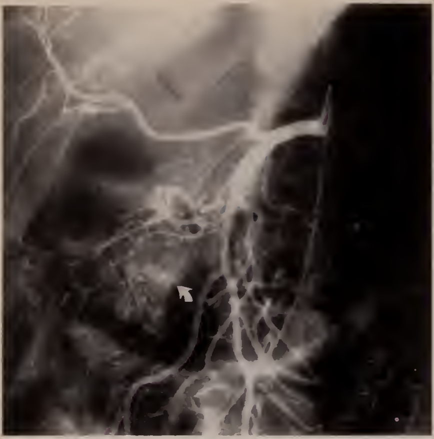


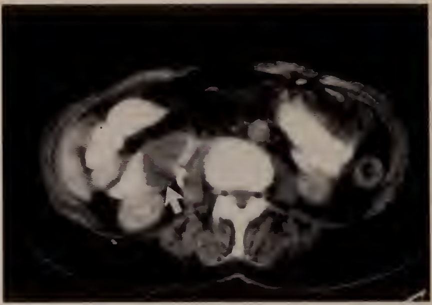
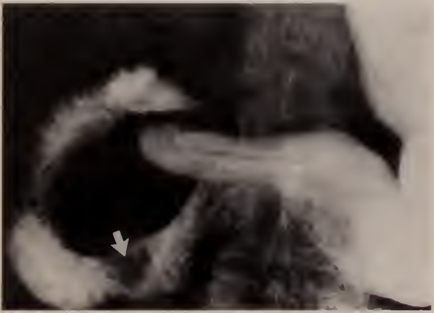


Fig. 1. Left Superior mesenteric artery angiogram demonstrating area of neovascularity in region of pancreatic head supplied by inferior pancreaticoduodenal artery (arrow). **Fig. 2. Right** CT scan demonstrating well-circumscribed solid mass adherent to third portion of duodenum. Dilatation of proximal duodenum is noted (arrow).



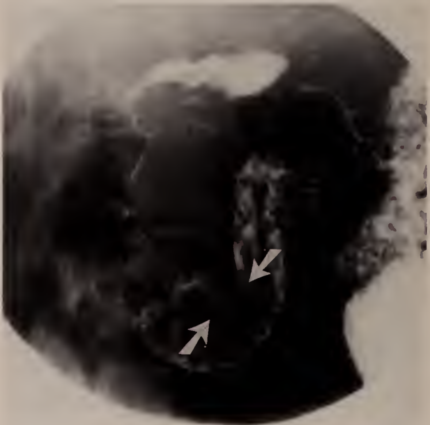


Fig. 3. Left Upper gastrointestinal series shows smooth extrinsic compression of duodenal sweep medially. Smooth filling defect is seen in region of papilla representing edematous protruded papilla secondary to compression by mass (arrow). **Fig. 4. Right** Air contrast portion of upper gastrointestinal series demonstrates protruded papilla (arrows).

In one series (6), routine upper gastrointestinal roentgenography was reported to miss 55% of the lesions because much of the tumor is frequently extraluminal. CT is particularly valuable in evaluating periampullary neoplasms and in determining whether a duodenal lesion is intrinsic or extrinsic. A leiomyoma is typically a homogeneous lesion of soft-tissue density on abdominal CT (7). Since the most common initial symptom of these tumors is bleeding, angiography has an important role in diagnosis. The angiogram can identify the size, location, and blood supply of the tumor. However, differentiation between benign and malignant tumors on the basis of tumor vascularity is usually not possible (8). Endoscopy is of limited value because most lesions are submucosal or subserosal but may be helpful when there is a central ulceration.

In this patient, the location of the lesion made it necessary to consider several alternatives in respect to its true nature, one of which was duodenal leiomyoma. Since the tumor was located near the papilla of Vater, an antral-sparing Whipple procedure had to be performed to remove it.

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Luteoma of Pregnancy

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LUTEOMA of pregnancy is an unusual ovarian lesion. It is a hormonally dependent, self-limited process, although it can be confused with a neoplasm. A case of multiple luteomata, discovered incidentally at cesarean section and initially thought to be a neoplasm on frozen section, is presented.

Case Report

A 38-year-old black woman, para 2002, underwent elective repeat cesarean section at term. An amniocentesis performed at 16 weeks gestation for advanced maternal age revealed a normal male infant. At the time of cesarean section, an enlarged solid right ovarian mass was noted. Frozen-section diagnosis suggested steroid cell tumor, possibly malignant. A right oophorectomy was performed. Urinary 17 ketosteroids and serum DHEAS performed 48 hours after surgery were within normal limits.

Pathological Findings. The ovary measured 8.5 × 7.0 × 3.0 cm. The external surface was dark purple and smooth. The ovary was predominantly solid, with some small surface cysts measuring up to 0.5 cm. On cut section, the ovarian parenchyma was tan, and contained three well-circumscribed red-brown nodules, measuring 5.5 × 5.5 cm, 3.2 × 2.2 cm, and 0.5 cm × 0.5 cm, respectively (Fig. 1). Histologically the lesions were composed of a uniform population of polygonal cells with abundant eosinophilic cytoplasm, and round nuclei containing prominent nucleoli. Mitoses were seen in many high-power fields (Fig. 2). In some areas the cytoplasm was more vacuolated. Electron microscopy revealed cytoplasm crowded with dilated smooth endoplasmic reticulum, stacks of rough endoplasmic reticulum, and abundant golgi and mitochondria with tubular cristae.

Discussion

Luteoma of pregnancy was first described by Sternberg in 1963 (1). It is a hormonally dependent, nonneoplastic lesion, probably arising from luteinized ovarian stromal cells (2), although some authors think it arises from luteinized granulosa and theca cells (3). It occurs during pregnancy and regresses with the puerperium. Although HCG is probably the most important inducing hormone, the rarity of luteomata in lesions with very elevated HCG levels, as in trophoblastic disease, suggests that this is not the only etiology of the condition (4).

As of 1984, 112 luteomata had been reported (3); an occasional subsequent report has appeared in the literature (5, 6). The lesions occur most often in the third and fourth decades, and are more common in black, multiparous women (7). Most are incidental findings at cesarean section or postpartum tubal ligation (8), a rare antenatal diagnosis being made (6).

Prenatal diagnosis of these tumors is uncommon for several reasons. The majority of lesions do not produce symptoms, unless they are hormonally active or undergo torsion. The large gravid uterus interferes with palpation of an adnexal mass, and may also prevent ultrasound detection. There has even been the suggestion that these lesions occur more commonly than they are diagnosed, since lesions in women who

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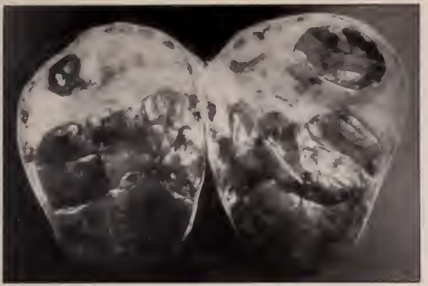
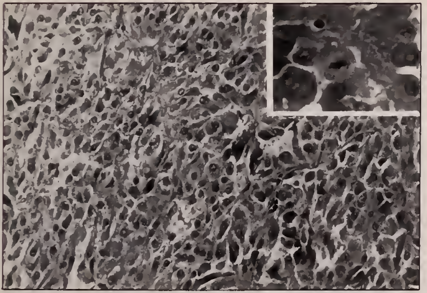


Fig. 1. Bisected ovary showing multiple red-brown nodules of luteomata.



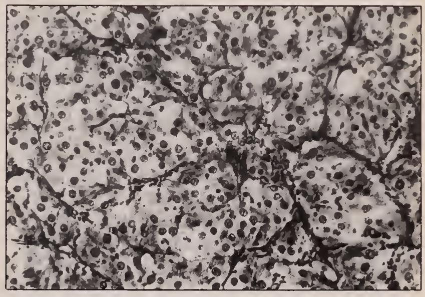


Fig. 2. **Left** Luteoma of pregnancy, with sheets of cells containing abundant cytoplasm (original magnification ×200). Note mitotic figure (inset, original magnification ×500). Fig. 3. **Right** Luteoma of pregnancy showing reticulin fibers surrounding groups of cells (reticulin, original magnification ×220). Steroid cell tumors show individual cells surrounded by reticulin fibers.

deliver vaginally are rarely detected (9). Some of the women with these lesions have increased urinary ketosteroids and increased plasma testosterone. This has sometimes resulted in masculinization of both mother, which may elicit prenatal studies, and female offspring (4). When a female fetus is spared masculinization, the placenta may have converted the androgens to estrogenic compounds (10).

Luteomata of pregnancy are characteristically soft and reddish tan, with frequent foci of hemorrhage, although the gross appearance is not unique to this lesion. They are bilateral in about a third of cases, and multinodular in approximately one half (7). Histologically, the lesion is composed of a population of large cells with eosinophilic cytoplasm, usually containing minimal or no lipid. Mitoses average 2 to 3 per 10 high-power fields. A reticulin stain reveals reticulin around groups of cells rather than around individual cells (8). Ultrastructurally, these lesions show features characteristic of steroid-hormone-producing cells, including abundant dilated smooth endoplasmic reticulum, golgi, stacks of rough endoplasmic reticulum, and mitochondria with tubular cristae (11).

Differential Diagnosis. Differential diagnosis includes other lesions with luteinized cells, such as luteinized thecoma, luteinized granulosa cell tumor, and steroid cell tumors. Luteinized lesions occurring during gestation, such as the luteinized follicle cyst of pregnancy, hyperreactio luteinalis, and the corpus luteum of pregnancy, are usually easily distinguishable. The first two are cystic in nature, as opposed to the solid luteoma. The corpus luteum of pregnancy has a characteristic lobulated appearance, with a mixture of two cell types, granulosa lutein and theca lutein cells.

Luteinized thecoma is solid and yellow-tan, but can appear similar histologically to luteoma, and can also be virilizing. However, its abundant reticulin, lipid, and areas of spindled cells usually aid in diagnosis. A luteinized granulosa cell tumor can grossly resemble a luteoma, but usually possesses areas that are composed of nonluteinized granulosa cells (12).

A more difficult distinction is with steroid cell tumors, as our case was initially thought to be. Both grossly and microscopically, they can be difficult to separate. Steroid cell tumors are a group of neoplasms previously called lipid cell tumor, lipoid cell tumor, hilus cell tumor, Leydig cell tumor, and stromal luteoma. They are all composed of cells resembling lutein cells, Leydig cells, and adrenal cortical cells.

Since many tumors do not, in fact, contain lipid, Scully devised a more concise working nomenclature (12). This classification includes (a) stromal luteoma, a small, entirely stromal surrounded neoplasm; (b) Leydig cell tumor, both hilar and nonhilar subtype containing Reinke crystalloids; and (c) steroid cell tumor NOS (not otherwise specified), for those that cannot be classed in either of the first two groups. Steroid cell tumors can be estrogenic, androgenic, or inactive, and may behave in either a benign or a malignant fashion (12).

Although even intraoperative distinctions can be difficult, factors that would favor a steroid cell tumor over luteoma of pregnancy include unilaterality, hilar location in some instances, single nodules, and microscopic findings of denser reticulin pattern (Fig. 3), Reinke crystalloids in Leydig cell tumors, lipochrome pigment, and intracellular lipid (10). Multiple nodules, mitoses, and absence of lipid favor the diagnosis of pregnancy luteoma. In some cases, a lipid-poor steroid cell tumor, NOS, occurring in a pregnant woman may be impossible to distinguish from a solitary pregnancy luteoma (8).

Summary

We have presented a case of luteoma of pregnancy, an uncommon ovarian lesion that is usually detected incidentally during cesarean section or postpartum tubal ligation. It is felt to be nonneoplastic, is hormonally stimulated, and regresses after childbirth. It is important to distinguish it from neoplastic lesions of the ovary that can occur in the same population, particularly steroid cell tumors, although this can be a difficult differential diagnosis.

Acknowledgments

The authors thank Glenn Maffei for photographic assistance.

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Editorial Note

Introducing Abstracts

THE Journal *is introducing a new feature in this issue: abstracts. Presented here are abstracts by principal investigators in the Department of Medicine of the Mount Sinai School of Medicine. All were exhibited in the department's Seventh Annual Research Day on September 12, 1989, a convocation of investigators who presented their work in posters much as they do in their subspecialty meetings. The day culminated in the oral presentation of four abstracts selected from the work of students, residents, and fellows working in the various laboratories of the department, which are widely dispersed throughout the School of Medicine (which includes the affiliates Beth Israel Medical Center, the Bronx Veterans Administration Medical Center, and Elmhurst Hospital Center).*

Only abstracts by principal investigators who have consented to publication in the Journal *are included. This selection adequately represents the breadth of the research performed under the aegis of the department.*

Future collections of abstracts will present the work of investigators in other departments and specialties at the Mount Sinai School of Medicine.—Robert Safirstein

Abstracts

Research Day in Medicine

Alcohol Research and Treatment Center

Intralobular Distribution of Ethanol-Inducible Cytochrome P450IIE1 in Liver M. Tsutsumi, M. Shimizu, J. M. Lasker and C. S. Lieber, Sect. of Liver Dis. & Alc. Res. Ctr., Bronx VAMC and Mt. Sinai Med. Sch., N.Y., N.Y.

Hepatic injury caused by chronic ethanol (E) intake starts and prevails in the perivenular (PV) area of the hepatic lobule. Since toxicity of E has been attributed to the metabolism of E, selective PV toxicity may reflect a zonal distribution of ethanol-metabolizing enzymes, either ADH or the P450IIE1 dependent microsomal ethanol oxidizing system (MEOS). The intralobular distribution of ADH is still disputed, but there is agreement on the lack of ADH inducibility by E.

Since P450IIE1 is highly inducible by E, we examined its hepatic introlobular distribution using immunohistochemical methods. A monospecific antibody (Ab) prepared against human liver P450IIE1 was utilized to stain liver sections from humans and from rats pair-fed liquid diets containing 36% of total energy as either E or carbohydrate (control; C). At low applied Ab (2:5 μg/ml), immunostaining was observed exclusively in the PV area in sections from E-treated rats, whereas no visible immunoreaction was found in C rats. These findings indicate that P450IIE1 induction by E occurs primarily in the PV zone. At higher applied Ab (15 μg/ml), panlobular immunostaining of P450IIE1 was observed in some of the E-treated rats, while in C rats, immunostaining was found exclusively in the PV area. The marked increase in P450IIE1 revealed by immunostaining was associated with a 10-fold rise in liver microsomal P450IIE1 was also observed immunohistochemically. Furthermore, protein blotting revealed that the P450IIE1 content in liver biopsies from alcoholics was 4-fold higher than in nondrinkers. Since the induction of P450IIE1 is associated with increased production of acetaldehyde free radicals, it may mediate much of the toxicity of E, thereby explaining the susceptibility of zone 3 to E-induced damage.

In conclusion, P450IIE1 is localized primarily in the PV zone of the hepatic acinus; its induction may contribute to the selective hepatotoxicity of E in zone 3.

Extrahepatic Localization of Ethanol (E)-Inducible P450IIE1 M. Shimizu, M.D., M. Tsutsumi, M.D., J. M. Lasker, Ph.D., C. S. Lieber, M.D. Alcohol Res. & Trtmt. Ctr., Bronx VA Med. Ctr. and Mt. Sinai Sch. of Med., NY, NY.

Liver microsomal P450IIE1 converts numerous environmental pollutants to toxic and/or carcinogenic metabolites. Since hepatic P450IIE1 levels increase as much as 10-fold after chronic E intake, an important role for this enzyme in chemical hepatotoxicity has been proposed, especially in alcoholics. E-potentiated tissue injury caused by certain xenobiotics that are P450IIE1 substrates also occurs in organs other than the liver. To determine the expression and inducibility by E of extrahepatic P450IIE1, frozen tissue sections were prepared from male rats pair-fed liquid diets containing 36% of energy as E or an isocaloric amount of antiperoxidase method after incubation with rabbit anti-human P450IIE1 IgG. The intensity of epithelial immunostaining, rated blindly from none (−) to intense (+ +), are given below (n = 4 pairs):

Extrahepatic Localization of Ethanol (E)-Inducible P450IIE1 *(continued)*

Tissue	Ethanol-fed	Control	Tissue	Ethanol-fed	Control
Oral mucosa	+	−	Jejunum	+	±
Tongue	+	−	Ileum	−	−
Esophagus	+	−	Colon	+	−
Stomach	−	−	Lung (bronchiolar)	+ +	+
Duodenum	+	±	Kidney (prox. tubule)	+ +	+

These data show that normally P450IIE1 is barely expressed in rat upper alimentary tract but that it can be induced by chronic E intake whereas constitutive P450IIE1 expression and E induction occurs in lung and kidney. Similar results were obtained on Western blots of extrahepatic microsomes immunostained with anti-P450IIE1 IgG.

In conclusion, E induces P450IIE1 in the upper GI tract (a primary site of entry for environmental toxins), which may partly explain why alcohol abuse is a risk factor for cellular damage and cancer in these tissues.

Characterization of the Increased Binding of Acetaldehyde (AC) to Red Blood Cells (RBC) in Alcoholics R. Hernandez-Munoz M.D., E. Baraona M.D., I. Blacksberg M.D. & C. S. Lieber M.D. Alcohol Res & Treatm Ctr, Bronx VA Med Ctr and Mt. Sinai School of Med, NY.

RBC play a major role in the transport of AC from the liver to peripheral tissues (Life Sci 40:253, 1987). AC could be reversibly bound to protein and nonprotein components of the RBC. To identify the binding to proteins, we used equilibrium dialysis at AC levels commonly occurring after ethanol ingestion (0–25 M).

There was no detectable binding to plasma proteins, but there was binding to RBC, more in alcoholics than in nonalcoholics. The AC-RBC binding was inhibited by pyridoxal phosphate and N-ethylmaleimide (NEM), suggesting adduction to amino and thiol groups. Binding kinetics were consistent with at least 2 sites. The one with the highest affinity for AC corresponded to hemoglobin (Hb). Its affinity was increased in alcoholics, but this was offset by decreased HB content, and its Bmax accounted for only 44% of the sites available in RBC of alcoholics and 80% of those in controls. Moreover, this binding was not inhibited by NEM. There was no detectable binding to RBC ghosts. Non-protein binding was assessed by changes in NADH produced by the addition of RBC protein-free fractions to an alcohol dehydrogenase system in equilibrium (Biochem J 225:565, 1985); this revealed a 2nd binder of lower affinity, larger capacity and with sensitivity to both inhibitors. This binding (possibly due to thiazolidine formation with cysteine) was enhanced in alcoholics, whose RBC cysteine content was doubled ($p < .005$). Levels of RBC cysteine and AC remained high until 2 weeks of withdrawal.

In conclusion, at concentrations commonly found in the blood after alcohol consumption, AC binds to Hb and to a nonprotein component of the RBC, presumably cysteine, which increases in alcoholics. The prolonged persistence of these changes after withdrawal may provide new biochemical markers of alcoholism.

S-Adenosyl-L-Methionine (SAMe) Attenuates Alcohol-Induced Mitochondrial Injury in the Baboon CS Lieber, LM DeCarli, C Kim, N Lowe, R Sasaki, MA Leo. Section of Liver Disease & Nutrition and Alcohol Research & Treatment Ctr., Bronx VA Medical Ctr. & Mt. Sinai School of Medicine, N.Y., USA

Chronic alcohol consumption results in striking mitochondrial damage, including ultrastructural changes, glutathione depletion and significant increases in the activity of plasma glutamic dehydrogenase (GDH), a mitochondrial enzyme. In an attempt to offset these alterations, SAMe, a glutathione precursor, was administered to baboons as part of a totally liquid diet (0.8 mg/kcal) with either ethanol (50% of energy) or isocaloric carbohydrate (controls).

In 10 baboons fed ethanol for 6–7 months, we observed the expected increase in plasma GDH (59.1 ± 14.7 IU/L vs 5.8 ± 0.9; $p < 0.005$), whereas in a corresponding group of animals given SAMe with ethanol, the values were only 32.8 ± 7.6 (vs 14.2 ± 2.7 in the SAMe-controls). After 15–18 months, the corresponding values were 95.1 ± 21.4 (vs 13.4 ± 1.8) and 30.3 ± 7.1 (vs 9.6 ± 0.7). This diminution in plasma GDH by SAMe ($p < 0.005$) was associated with a decrease in liver GDH and in the number of giant mitochondria (assessed in percutaneous liver biopsies), with a corresponding change in succinic dehydrogenase (SDH), a mitochondrial marker enzyme. SDH activity was increased in liver homogenates of ethanol-fed animals (82.8 ± 3.8 mU/mg protein vs 52.7 ± 2.7 in controls; $p < 0.001$), probably reflecting the increased mitochondrial mass. SAMe attenuated ($p < 0.005$) this effect (66.0 ± 5.8 in SAMe-ethanol vs 44.0 ± 1.9 in SAMe-controls). The hepatic glutathione depletion produced by ethanol (2.7 ± 0.2 mol/g vs 5.1 ± 0.4 in controls; $p < 0.01$) was also partly corrected (3.6 ± 0.7 in SAMe-ethanol vs 4.9 ± 0.8 in SAMe-controls). The latter effect could be responsible for some of the beneficial actions of SAMe reported here.

In conclusion, SAMe administration significantly reduced the number of ethanol-induced giant mitochondria, the corresponding increase in mitochondrial mass (as reflected by hepatic SDH) and the associated rise in plasma GDH, possibly by offsetting glutathione depletion.

Cardiology

Percutaneous Excimer-Laser-Assisted Coronary Angioplasty Sabino R. Torre MD, Timothy A. Sanborn MD, Ronnie A. Hershman MD, Warren Sherman MD, Marc Cohen MD, John A. Ambrose MD, Division of Cardiology, Mt. Sinai Medical Center, New York, NY.

Percutaneous excimer-laser-assisted coronary angioplasty may serve as a useful adjunct or alternative to conventional percutaneous transluminal coronary angioplasty. Excimer lasers are pulsed gas lasers that use a mixture of a rare gas and halogen (i.e. XeCl) as the active medium to generate pulses of short wavelength, high energy, ultraviolet light. Experimental applications of excimer laser energy to atherosclerotic vascular stenoses have resulted in successful ablation of complex atherosclerotic plaques without evidence of neointimal thermal injury. This feature of excimer laser energy may prove useful in reducing the rate of restenosis after successful percutaneous revascularization. This study was designed to determine the feasibility and potential for percutaneous excimer laser assisted coronary angioplasty.

A total of fourteen patients underwent percutaneous excimer-laser-assisted coronary angioplasty. Fourteen coronary artery stenoses (9 LAD, 4 RCA, 1 LCx) were first treated with a XeCl (308 nm) excimer laser with a pulse width of 120 nanoseconds, energy fluence of 30–45 mJ/mm^2 and repetition rates of 25–40 Hz followed by conventional balloon angioplasty. Excimer laser energy fully recanalized 10 stenoses, partially recanalized 2 stenoses, and had a minimal effect on 2 stenoses without evidence of laser related adverse effects such as perforation, spasm or thrombosis. Four complications attributed to balloon angioplasty occurred including an elevation in CPK without Q-waves in two patients secondary to distal microembolization and branch occlusion respectively, an acute proximal coronary thrombosis related to the guiding catheter, and restenosis of the dilated segment at 48 hours. Angiographic results are summarized below:

Percutaneous Excimer-Laser-Assisted Coronary Angioplasty *(continued)*

	Stenosis (%)		Vessel diam. (mm)	
	mean	range	mean	range
Pre-laser	80	62–95	0.58	0.21–1.1
Post-laser	51*	19–83	1.35*	0.41–2.6
Post-PTCA	14*	0–26	2.41*	1.60–3.2

*$p < 0.001$

This study demonstrates the feasibility of percutaneous excimer laser assisted coronary angioplasty. This technique may prove to be a useful adjunct or alternative to conventional balloon angioplasty. Future directions include modifications of the laser system and long term trials.

Predictors of Delayed (24 hr) Redistribution of Early "Fixed" Defects on Exercise SPECT Thallium Imaging Samin Sharma, M.D., Dimitrios Alexopoulos, M.D., Josef Machac, M.D., Division of Cardiology, Box 1030, Mount Sinai Medical Center.

We wished to find clinical and imaging predictors of thallium delayed (24 hr) redistribution to avoid 24 hr imaging in patients with fixed early (3 hr) defects. SPECT Thallium images of 77 patients with 210 3 hr essentially fixed defects and available 24 hr images were read by an experienced reader on a 5 point scale in 5 regions. A history of MI, regional Qwaves, exercise ST changes, exercise chest pain, minimal early redistribution and severity of the 3 hr defects were tested singly and by stepwise logistic regression for their predictive value (+PV, −PV) for delayed redistribution and complete 24 hr delayed redistribution.

A history of MI, chest pain with exercise, severity of 3 hr defects and minimal early redistribution had significant predictive power for delayed redistribution, but the negative predictive value was only 61–65% and the positive predictive value was 60–69%. All tested variables had significant predictive power for complete redistribution, but a positive predictive value of only 18–48%. The clinical variables and 3 hr defect severity were found useful by stepwise logistic regression. At 80% level of confidence, 41 (35%) 24 hr fixed defects, 49 (53%) delayed redistribution and 16 (42%) complete redistribution were predicted by the model.

Thus, clinical and image variables alone could not predict delayed redistribution in all pts. The stepwise logistic regression model found that 43% of 3 hr fixed defects did not need 24 hr imaging (24 hr fixed defects 20%, delayed redistribution 23%).

Left Ventricular Mass Regression and Improved Left Ventricular Filling in Severe Hypertensives Treated with Nifedipine Robert A Phillips MD PhD, Maria Ardeljan RN, Martin E Goldman MD, Lawrence R Krakoff MD. Divisions of Hypertension and Cardiology, Box 1085, Mount Sinai Medical Center, NY, NY.

Reversal of two of the more serious complications of hypertension, left ventricular (LV) hypertrophy and abnormal LV filling, has not previously been reported in patients with severe essential hypertension.

We treated 20 severe hypertensives (diastolic blood pressure (BP) >120 mm Hg, age 54 ± 4, mean ± s.e.m.) with long-term monotherapy using a once-a-day continuous release preparation of nifedipine. Serial measurements by echo/Doppler to assess LV mass index (LVMI) and LV filling were made at entry (E) when average BP was 189 ±/117 ± 3, after titration (T) of diastolic (BP) to <95 mm Hg (average BP = 149 ± 6/90 ± 3) and after two months (2 M) of sustained blood pressure (BP) control. The ratio of atrial to early LV filling velocity (A/E ratio) was used as an index of LV filling. At E, 56% had elevated LVMI and 60% had an elevated A/E ratio. At 2 M, LVMI was significantly reduced from 127 ± 8 to 115 ± 9 gms/m^2, $p < 0.01$. LVMI regression was not correlated with the fall in BP but was directly correlated with the fall in norepinephrine ($r = 0.54$, $p < 0.05$). LV filling improved significantly with a fall in the A/E ratio from T to 2 M (1.4 ± 0.2 vs 1.2 ± 0.1). Patients with the worst LV filling prior to sustained BP reduction had the greatest improvement with treatment. There

Left Ventricular Mass Regression and Improved Left Ventricular Filling in Severe Hypertensives Treated with Nifedipine ***(continued)***

was no relationship between LVMI regression and improved LV filling.

Conclusion: In severe hypertension sustained BP reduction with nifedipine is accompanied by LV mass regression and improved LV filling, but these responses may be dissociated.

Ventricular Tachycardia Associated with Sarcoidosis: The Anatomic Substrate, Natural History, and Role of the Automatic Implantable Cardioverter Defibrillator Stephen L. Winters, M.D., Steven Greenberg, M.D., Pramod Deshmukh, M.D., Elena Pe, R.N., Marc Cohen, M.D., Josef Machac, M.D., J. Curwin, M.D., Mark J. Rosen, M.D., J. Anthony Gomes, M.D. The Mount Sinai Medical Center, Division of Cardiology, Box 1054, 1 Gustave L. Levy Place, New York, NY.

Whereas atrioventricular block is a recognized rhythm disturbance in pts with sarcoidosis, sudden death due to ventricular tachycardia (VT) has not been systematically assessed. Thus, we evaluated 7 pts (mean age: 38 yrs) with documented ventricular tachycardia in association with sarcoidosis. All pts underwent noninvasive cardiac evaluations in addition to attempts at guidance of antiarrhythmic drug administration with programmed ventricular stimulation (PVS). Two of the 7 pts (29%) had VT as the initial manifestation of sarcoidosis. Pulmonary involvement was present in 3 pts, uveitis in 2 pts, and lupus pernio in 1 pt. Four pts had focal left ventricular (LV) dyskinesis, 1 pt had localized LV hypokinesis, and 1 pt had diffuse LV hypokinesis. The mean LV ejection fraction was 35%. Three of the 6 pts (50%) who had echocardiograms performed had mitral valve prolapse and/or mitral regurgitation present.

Natural History: After a mean of 4 antiarrhythmic drug trials, PVS demonstrated control of VT in 4 (57%) pts. One pt refused (age 25 years) follow-up electrophysiologic testing, was discharged on Holter monitor-guided therapy with quinidine sulfate, and had sudden death within 2 months. A second pt (age 30 years) had sudden death after 18 months of electrophysiologic-guided antiarrhythmic drug therapy. Of the other 5 pts, 1 has remained free of documented sustained VT after 12 months of antiarrhythmic drug therapy found to be suppressive of induction of VT at PVS. Two pts with recurrent VT underwent implantation of automatic cardioverter-defibrillators. The other 2 pts had automatic cardioverter-defibrillators implanted as early therapy, regardless of drug suppression of inducible VT. The 4 pts with implanted automatic cardioverter-defibrillators have had shocks delivered and remain alive for a mean of 11 months since detection of VT.

Conclusions: 1. Focal left ventricular dyskinesis, mitral valve prolapse, and/or mitral regurgitation are associated with ventricular tachycardia in pts with sarcoidosis; 2. antiarrhythmic drug therapy of ventricular tachycardia in pts with sarcoidosis is associated with a high rate of recurrence of ventricular tachycardia or sudden death; 3. the implantable cardioverter-defibrillator should be considered as early therapy of ventricular tachycardia in pts with sarcoidosis.

Quantitative Analysis of the Admission Electrocardiogram Predicts Outcome in Patients with Rest Angina Marc Cohen, M.D. Linda Hawkins, R.N., Steven Greenberg, M.D., Valentin Fuster, M.D., Division of Cardiology, Box 1030, Mount Sinai Medical Center.

A retrospective study to determine the reliability of the admission ECG in predicting clinical outcome in patients (pts) with rest angina, we studied 90 pts who were randomized to a trial of aspirin versus heparin in unstable angina and followed for 3 months.

The ΣST segment deviation and the total number of leads (NOL) with ST or T wave changes were measured from the admission ECG. 62 pts had pain during the admission ECG and 28 did not; 10 pts had LVH by ECG. Clinical events consisted of recurrent ischemic pain, infarction, and PTCA or CABG for recurrent pain or compelling anatomy. Considering all 90 pts; an admission ECG with ΣST ≥ 2 mm *and* NOL ≥ 2 had a + predictive value for clinical events of 79%. An ECG with ΣST <2 *or* NOL <2 had a −predictive value of 64%. Excluding pts with LVH, or without pain during the ECG, the +predictive value improved to 87% and the −value to 71%.

Quantitative Analysis of the Admission Electrocardiogram Predicts Outcome in Patients with Rest Angina ***(continued)***

Conclusion: In pts with unstable angina, an admission ECG recorded during pain, showing ischemic changes, is by itself a reliable predictor of major clinical events. Conversely, a "benign" ECG during pain correctly identifies pts with a benign clinical course in the majority of cases, but does not necessarily exclude recurrent ischemia or intervention.

Effect of Canola Oil Addendum upon Blood Pressure and Serum Lipids in Humans Robert P. Reichstein, M.D., Marvin L. Bierenbaum, M.D., William P. Maginnis, Ph.D., Thomas P. Watkins, Ph.D. Division of Cardiology, Department of Medicine, 5 East 94th Street, New York, NY.

Recent work has been done using fish oil supplements as an antilipemic, platelet anti-aggregant and antihypertensive. Several shortcomings of this approach have led to the search for terrestrial sources of omega 3 fatty acids able to produce similar effects.

Attempting to evaluate possible effects upon blood pressure (BP) and blood lipids (L), 22 normotensive, hyperlipemics were fed a daily supplement (30 g) of canola oil along with their self-selected diets. The oil contained (wt.%): oleate, 62; linoleat, 22; and α-linolenate, 10. After a four-week baseline period, subjects included the oil with meals. Preliminary RBC acyl data indicated that oil was consumed appropriately. Mean weights did not change. Neither systolic BP, 125 vs. 126, nor diastolic BP 97.3 vs. 97.2, changed (mmHg, baseline vs. test). Though mean total CHOL did not change significantly (270 vs. 264 mg/dl), the LDL cholesterol decreased from 193 to 178 mg/dl by the end of the 16-week supplementation period, $P < 0.05$, in contradistinction to fish oils which appear to raise LDL cholesterol. Serum triglyceride did not change.

These data suggest that canola oil may have promise in dietary strategies to reduce serum LDL cholesterol, perhaps at higher doses incorporated into oil-bearing food products.

Is Myocardial Dysfunction Regional or Diffuse in Aortic Regurgitation? S. F. Horowitz, J. Vassiliadis, J. Machac, D. Matza, D. Alexopoulos, M. D. McGoon, and R. J. Gibbons. Mount Sinai Hospital, NY, NY and The Mayo Clinic, Rochester, MN.

Previous studies have suggested that apical asynergy is a common feature of LV dysfunction associated with aortic regurgitation (AR). We performed rest (R) and exercise (Ex) gated blood pool imaging on 61 patients with AR of varying degrees of severity, and 10 normals. Three regional ejection fractions (EF) were obtained in the LAO view for R and Ex: septum (S), inferoapex (A) and posterolateral wall (P). Patients were divided on the basis of resting EF(REF). Results were compared by ANOVA for differences at R and Ex.

Class	S EF	A EF	P EF	S EF	A EF	P EF
REF $\leq$ 45	35 ± 15	49 ± 18	45 ± 18	−9 ± 16	−3 ± 22	−2 ± 23
45 $\leq$ REF $\geq$ 55	38 ± 6	57 ± 7	50 ± 4	0 ± 10	3 ± 14	3 ± 11
REF $\geq$ 55	46 ± 11	69 ± 10	59 ± 7	−1 ± 12	5 ± 12	2 ± 14
Normal	42 ± 10	74 ± 8	54 ± 9	14 ± 15	17 ± 11	22 ± 13

Effects:

Class	p = 0.0001	Class	p = 0.0001
Segment	p = 0.0001	Segment	p = 0.0001
Class∗Segment	p = 0.0002	Class∗Segment	p = 0.51

In the present study, regional quantification suggests that increasing severity of disease results in a greater decrease in A function relative to S and P at rest compared to normals. With Ex, the S tends to enhance less than A or P but this change is proportional in AR and in normals. The subjective perception of regional asynergy in AR is supported at rest. However, exercise-induced effects appear to be global.

Serial Changes in Left Ventricular Function in Patients with Mitral Regurgitation. Josef Machac, M.D., Deborah Matza, R.N., Michael McGoon, M.D., Dimitrios Alexopoulos, M.D., Raymond Gibbons, M.D., Martin E. Goldman, M.D., Steven F. Horowitz, M.D., Division of Cardiology, Box 1030, Mount Sinai Medical Center. and The Mayo Clinic, Rochester, MN.

We studied 26 patients with pure mitral regurgitation (MR) using rest and exercise gated blood pool imaging at baseline (T_0) and one-year follow-up (T_1). Patients were evaluated for changes in left (LV) and right (RV) ventricular ejection fraction (EF), work load and NYHA class.

Resting LVEF decreased from .60 ± .07 at T_0, to .55 ± .10 at T_1 (P = .007). There were no serial changes in exercise LVEF (.58 ± .11 vs .56 ± .09, P = NS), rest RVEF (.32 ± .12 vs .30 ± .11, P = NS), or exercise RVEF (.36 ± .12 vs .35 ± .12, P = NS). Work load fell slightly (96 ± 42 vs 88 ± 35, P = .08, watts). There were no changes in NYHA class (1.3 ± 0.6 vs 1.3 ± 0.5, P = NS) between T_0 and T_1.

We divided patients by median regurgitant index into high and low groups. At T_0 there were no differences in LVEF at rest or exercise. RVEF was lower in the high regurgitant index group at rest (.26 ± .12 vs .38 ± .10, P = 0.01) and exercise (.32 ± .13 vs .39 ± .11) but did not reach significance at exercise, (P = NS).

Conclusion: In this group of mitral regurgitation patients followed for 1 year, LVEF declined significantly despite absence of clinical deterioration.

Clinical Immunology

Localization and Potential Mechanism of the Expansion of T Cells Bearing Specific T Cell Receptor V_β Gene Products in Patients with Crohn's Disease I Schmelkin, L Mayer and DN Posnett. Divisions of Clinical Immunology and Gastroenterology, Mount Sinai Medical Center and New York Hospital, New York, NY.

We have recently observed that there is a selective increased usage of a T cell receptor (TcR) β chain variable region gene product designated Vβ8 (detected by monoclonal antibody (mAb)Ti3a) on peripheral blood (PB)T cells in about 25% of patients with Crohn's disease (CD). Similar increases were not observed in either normal controls or patients with ulcerative colitis (UC). In order to further investigate the preferential expression, mechanism, and genetics behind this phenomenon, we performed the following studies: Cells were isolated from a variety of intestinal tissues and analysed for the presence of Vβ8 bearing T cells. Enrichment of $V\beta8^+$ T cells were noted in tissue sections as well as isolated mesenteric lymph node(MN) T cells from patients with CD (n = 10, range 4.2–22%, mean = 8.6%). No increase in $V\beta8^+$ T cells were detected in MN T cell from normals (n = 3, range 1–2.2%, mean = 1.6) or patients with UC (n = 5, range 1.6–4.6, mean 2.8%). In contrast, no difference in $V\beta8^+$ T cells between normals, CD, or UC were detectable in lamina propria cells either freshly isolated or on tissue sections suggesting that expansion of $V\beta8^+$ T cells might relate to an efferent limb immune response.

Since antibody to TcR can induce selective expansion of clonal T cell populations, we next tested the possibility that Ab to Vβ8 exists in the serum of patients with CD. Serum from 2 patients, with elevated $V\beta8^+$ T cells reproducibly induced the proliferation of $V\beta8^+$ T cells in normal PB T cell populations. Furthermore, antibodies isolated from mitogen stimulated MN lymphocytes (from MN with increased $V\beta8^+$ cells), specifically stained the $V\beta8^+$ T cell line Jurkat, suggesting that anti-TcR Ab might be responsible for the observations described. Relevant to this was the finding that mAb Ti3a, but not isotype controls or an anti-CD3 mAb, detected a cross-reactive (? auto-) antigen on the surface of all intestinal epithelial cells, which did not correspond to the molecular weight of TcR (determined by immunoprecipitation). Finally, in order to determine if this phenomenon is under a primary genetic influence, 11 families werre studied in which the index CD patient had elevated $V\beta8^+$ T cells. In only one family could we detect an increase in PB $V\beta8^+$ T cells (24%) in the unaffected father of a patient with CD ($V\beta8^+$ T cells = 22%).

Despite the presence of more than one affected individual in other families, no consistent increase in $V\beta8^+$ T cells was detected, suggesting that the response seen relates to a local immune response rather than linkage to an immune response gene.

Localization and Potential Mechanism of the Expansion of T Cells Bearing Specific T Cell Receptor V_β Gene Products in Patients with Crohn's Disease *(continued)*

Autologous Anti-Anti Kappa Casein Antibodies in IGA Deficient and Normal Sera C. Cunningham-Rundles and Zhi-Kun Feng Clinical Immunology, Box 1089, Department of Medicine, The Mount Sinai Hospital.

There is scant information available about the prevalence and characteristics of auto anti-idiotypic antibodies in human systems. In a previous study, we showed that autologous anti-anti bovine casein antibodies could be isolated from the sera of two IgA deficient individuals and that a mixture of bovine caseins could block the binding of the idiotype and the autologous anti-idiotype. To define the specific anti-idiotypes involved, we turned to the use of monoclonal anti kappa -casein antibodies, since kappa casein is an important immunogen for humans, and has a known amino acid sequence, and a limited number of antigenic epitopes.

Data presented show that the serum of many IgA deficient and some normal serum have specific autologous anti-idiotypes in their serum which bind to monoclonal antibodies (4.3 and B5) directed to bovine kappa casein. The autologous anti-idiotypes behave as potential "internal images," or Ab2 as defined by Jerne, and each can be blocked from binding to the monoclonal anti-kappa casein antibodies (Ab1) by the same amino-terminal peptide of bovine kappa casein which is the target of the monoclonal antibodies themselves.

For IgA deficient individuals and age matched controls, serum levels of the auto anti-idiotype were directly proportional to the level of IgG antibody to bovine kappa casein, and for IgA deficient subjects, both Ab1 and Ab2 declined with increasing age. Previous experiments of autologous anti-idiotypes in sera of patients with autoimmune disease have demonstrated a reciprocal relationship between the amount of Ab1 and Ab2, but it is unknown whether any previous model can be applied to a human system in which continuous antigen exposure occurs.

Failure to Confirm Standard HLA and GM Immunogenetic Typing as a Predictor of Familial Autoimmune Thyroid Disease S. H. Roman, M. Hubbard, and P. Rubenstein, Department of Medicine and Department of Biomathematical Sciences, Mount Sinai School of Medicine and Laboratory of Immunogenetics, New York Blood Center, New York, NY.

The combination of HLA and immunoglobulin (IgG) heavy chain allotypes (Gm) has previously been reported to be predictive of autoimmune thyroid disease (ATD) in selected Japanese families but has not been evaluated elsewhere.

We have investigated immunogenetic markers in 30 families (n = 126) with multiple instances of ATD. HLA-A, -B, and -C antigens were tested with a modified NIH microlymphocytotoxicity technique and HLA-DR antigens were tested with the two color fluorescence test. The major Glm specificities a(1), x(2), and f(3) were determined with standard hemagglutination inhibition techniques. There were 11 families with multiple instances of ATD among siblings, includin 5 sib pairs with Hashimoto's thyroiditis, 3 sib pairs with Graves' disease, and 3 sib pairs with mixed disease i.e. one sib having Hashimoto's thyroiditis, the other Graves' disease. For each family, HLA and Gm identity was determined by those antigens associated with ATD in other generations. The distribution of HLA and Gm identity between sib pairs was:

	HLA identical	HLA nonidentical
Gm identical	4 sib pairs	4 sib pairs
Gm nonidentical	2 sib pairs	1 sib pair

p = NS by McNemar's Test

HLA and Gm identical pairs consisted of 2 Graves' disease pairs, 1 Hashimoto's thyroiditis and 1 mixed pair.

In conclusion, HLA and Gm identity was present in only 4/11 (36%) ATD sib pairs in families selected for multiple instances of ATD.

Failure to Confirm Standard HLA and GM Immunogenetic Typing as a Predictor of Familial Autoimmune Thyroid Disease *(continued)*

In contrast to previous reports, we found HLA and Gm immunogenetic markers, determined by standard immunotyping techniques, to be inadequate predictors of ATD in highly affected (multiplex) families. Familial studies at the DNA level may be more informative.

Interleukin 6 Induces Primitive Lymphoid Gene Expression in Mast Cell Lines Derived from the Murine Embryo prior to the Colonization of the Primary Lymphoid Organs Edward J. Siden, Division of Clinical Immunology, The Mount Sinai Medical Center, New York, NY.

In an effort to generate tumor cell models of the earliest stages of hematolymphoid development, we established cell lines from the murine embryonic placenta. This tissue is contiguous with the embryonic yolk sac and was reported to contain B lymphocyte precursors before their appearance in the fetal liver. Cell lines derived by viral-transformation with Abelson murine-leukemia virus (Ab-MuLV) were generated by infection of a population of cells only found in the embryo from 10–12 days of gestation, just before lymphoid colonization of the fetal liver and thymus. While cell lines derived by Ab-MuLV infection of fetal liver have traits expected of early B cell precursors, including early B cell differentiation antigens, antibody gene transcription and rearrangement, the cell lines generated from the earlier embryo all have multiple characteristics of mucosal or culture-derived mast cells. While this unexpected cell phenotype is typically thought to be the terminally differentiated cell of a unique cell lineage, we have previously shown that many of the lines express both primitive B and T cell surface antigens and that some express mRNA from germline immunoglobulin heavy chain variable region genes. In addition, we found that BUdR, an anti-proliferative drug, induced the synthesis of RNAs transcribed from germline immunoglobulin mu and T cell receptor gamma constant region loci as well as upregulated the mRNA for the B cell surface protein, B220. While this intriguing observation suggests the potential for mast cells to differentiate into lymphocytes, the system is still far from physiological.

We have now observed that the mast cells respond to the physiologically relevant hormone Interleukin 6 (IL-6) with the same spectrum of new gene expression that was observed with BUdR. Experiments are in progress to identify analogous normal cells in the embryo and to test their developmental potential.

Generation of Human Macrophage Hybridomas *(continued)* K. Sperber, A. Pizzamenti, J. Bauer, V. Najfeld, A. Shaked, L. Mayer. Division of Clinical Immunology, Mount Sinai School of Medicine.

Macrophages play an essential role in normal host defense and are vital as antigen presenting cells in the generation of an immune response to antigen. These cells are the product of a maturation process of peripheral blood monocytes derived from bone marrow precursors. The lack of available macrophage cell lines has hampered understanding of their vital functions. Our laboratory has previously generated human monocytes hybridomas by fusing monocyte obtained from peripheral blood by counterflow elutriation with a HAT sensitive promonocytic line U937. These hybridomas have many normal monocytes characteristics including expression of monocyte markers and Class II antigens not present on U937, cytokine secretion, ability to stimulate in a mixed lymphocyte reaction and antigen processing.

To extend our studies to macrophages we have generated a series of macrophage hybridomas by fusing a HAT sensitive U937 with macrophages obtained by allowing peripheral blood monocytes to mature into macrophages in Teflon bags. The result of these fusions was the generation of 15 macrophage lines. These cell lines represent a more mature monocytic cell type and differentially express the normal macrophage markers, Vmax.1, Vmax.2, Vmax.3 and Vmax.11 which are not present on U937 or on the monocyte hybridomas. There is differential expression of the ICAM molecules and two cells lines, 38 and 39, grow adherently. In contrast to the monocyte hybridoma lines, there is increased expression of Class II molecules [2 of 11 lines vs. 13 of 13 of 15 lines]. IL-1 is synthesized in 10-fold greater concentration in the macrophage lines compared to the monocyte lines as assessed by D-10 proliferation after LPS stimulation. One clone, 63, secretes 2 mucous secretogogues after LPS stimulation.

Generation of Human Macrophage Hybridomas *(continued)*

Macrophages as well as monocytes are capable of serving as fusion partners to generate hybridomas. Our macrophage cell lines, which differ significantly from monocyte cell lines, will serve as a useful model system in which to study normal macrophage functions.

Differential Secretion of IL2 and γ-IFN by Lamina Propria Lymphocytes from Normals and Patients with Inflammatory Bowel Disease (IBD) P. Solomon, A. Reisman, A. Panja, and L. Mayer. Divisions of Clinical Immunology and Gastroenterology. Mount Sinai Medical Center.

We have previously shown that whereas normal intestinal epithelial cells selectively activate suppressor T cells in accessory cell/T cell interactions, there appears to be a defect in accessory cell function in the epithelium of patients with IBD whereby helper T cells are activated. We have postulated that, during this activation process, nonspecific lymphokines may be secreted which in turn activate other local cell populations (i.e. macrophages, B cells) resulting in the release of nonspecific mediators of inflammation. Lamina propria lymphocytes (LPLs) are cells which have the potential for direct interaction with the overlying epithelium.

In order to assess the panel of lymphokines secreted by these cells, we isolated LPLs and cultured them alone (to assess spontaneous secretion) or in the presence of the nonspecific T cell mitogen PHA (to assess induced secretion). IL2 and γ-IFN secretion were measured after 48 h by standard bioassays. No spontaneous secretion of either cytokine was detected in LPL cultures from normals or patients with IBD. However differences were detected in supernatants of T cell stimulated with PHA. In general, γ-IFN secretion was increased in LPL cultures from patients with IBD (both CD and UC) compared with normals although some variability was noted. Furthermore, γ-IFN secretion was greater in LPLs isolated from involved areas vs. more histologically normal areas. In contrast, no significant differences were detected in the secretion of IL2 between normals and IBD patients.

Since γ-IFN is a potent inducer of class II antigen expression on epithelial cells and monocytes and monokine and superoxide secretion from macrophages, these data suggest that LPLs from patients with IBD may be playing an important role in the inflammatory processes seen in these diseases. Interruption of γ-IFN secretion may therefore be a valid avenue of therapeutic intervention in IBD.

Cyclosporin Has a Direct Effect on B Lymphocytes: Inhibition of B Cell Growth and Differentiation Mediated by Cytokines M. Cidon, D. Sherris, and L. Mayer. Division of Clinical Immunology, Mount Sinai Medical Center.

Cyclosporin (Csa) has become a critically important agent used for immunosuppression in organ transplantation. The mechanism of action of this drug is thought to be mediated by its ability to inhibit IL2 secretion by activated T cells thereby inhibiting the generaton of cytolytic T cells against the graft. We have recently described two novel lymphokines, derived from anti-CD3 stimulated T cells which mediate resting B cell proliferation (BCPF) and activated B cell differentiation (BCDF). Since Csa is able to inhibit lymphokine production by activated T cells we wanted to determine whether BCDF and BCPF were cyclosporin sensitive.

Supernatants were generated from normal T cells activated with anti-CD3 mAbs in the presence or absence of Csa, and tested for their ability to induce B cell proliferation, measured by ^{3}H thymidine incorporation, or differentiation, measuring immunoglobulin secretion by ELISA. BCPF secretion was maintained even in the presence of Csa whereas there was a marked inhibition of BCDF activity. Part of this inhibition could be explained by a direct effect of Csa on B cells, as exogenous Csa was able to inhibit B cell differentiation in response to purified BCDF. A lesser although significant decrease in B cell proliferation was also noted when Csa was added directly to B cell cultures stimulated with BCPF. The inhibition in both cases was dose dependent and could not be explained by changes in the viability of the B cell population.

Therefore there appears to be differential regulation of T cell lymphokine secretion, measured by Csa sensitivity, suggesting the presence of distinct activation signals. In addition, B cells as well as T cells

Cyclosporin Has a Direct Effect on B Lymphocytes: Inhibition of B Cell Growth and Differentiation Mediated by Cytokines *(continued)*

appear to be sensitive to he effects of Csa, suggesting a dual inhibitory pathway as a mechanism in the immunosuppression observed with this agent.

Endocrinology

Does Hyperandrogenemia Sustain Insulin Resistance (IR) in the Polycystic Ovary Syndrome (PCO)? A. Dunaif, W. Futterweit, G. Green, I. Tattersall, and A. Dobrjansky, Mount Sinai School of Medicine, New York, NY.

PCO women have significant IR and are at risk to develop non-insulin dependent diabetes mellitus (NIDDM). The role of hyperandrogenemia in the pathogenesis of IR in PCO thus has important clinical as well as physiologic implications. Previous studies of this issue have been inconclusive because of small sample sizes and imprecise measurements of IR. Hence we performed 2 h euglycemic insulin (~100 uU/ml) clamps in 9 PCO women with IR basally and after the 12th week of therapy (Rx) with a superagonist GnRH analogue (GnRHa, [(imBzl)-D-His^6, Pro^9-NEt]GnRH), 40 µg sq q 8 h. Diet, activity, and weight were kept constant. Comparisons by paired analyses, mean ± SE:

	Basal	Rx	P		Basal	Rx	P
BMI[a]	35.6 ± 2.6	35.6 ± 2.7	NS	M[e]	2.10 ± .40	2.04 ± .40	NS
T[b]	55 ± 13	23 ± 3	.01	IRI[f]	45 ± 8	37 ± 4	NS
A[c]	214 ± 30	106 ± 15	.02	MCR[g]	443 ± 54	532 ± 39	.07
DHEAS[d]	243 ± 36	226 ± 33	NS	HGP[h]	69 ± 4	66 ± 3	NS

Key & normal ranges obese women: [a]body mass index > 28 kg/m^2; [b]testosterone 11–44 ng%; [c]androstenedione 42–176 ng%; [d]dehydroepiandrosterone sulfate 70–340 ug%; [e]insulin-stimulated glucose disposal 2.50–5.00 mg/kg/min; [f]basal insulin 8–28 uU/ml; [g]metabolic clearance rate of insulin 373–669 ml/m^2/min; [h]basal hepatic glucose production 49–63 mg/m^2/min

The sample size was adequate to detect a clinically significant change in M (i.e. ~0.60 mg/kg/min) at $P \leqslant 0.05$. Further, 385 PCO women would have been required to determine whether the observed mean difference in M (0.06 mg/kg/min) was significant at $P \leqslant .05$.

We conclude that 1) suppressing androgen levels into the normal range did not result in significant changes in IR in PCO; 2) disordered LH/FSH release rather than hyperinsulinemia was the primary cause of hyperandrogenemia in PCO since it was possible to suppress androgen levels with GnRHa without changing IRI levels; 3) hyperandrogenemia might have decreased the MCR of insulin; and 4) controlling hyperandrogenemia is not a clinically effective modality to improve insulin action and thereby decrease the risk of NIDDM in PCO.

LH-Secreting Adenoma Presenting with Galactorrhea-Amenorrhea in an 18-Year-Old Woman W. Futterweit, M.D., N. S. Halmi, M.D., J. I. Mechanick, M.D., and S. K. Song, M.D., Division of Endocrinology, Department of Medicine, and Department of Neuropathology, Mount Sinai School of Medicine, New York, NY.

Gonadotropin-producing pituitary adenomas represent 3–17% of all pituitary tumors. Isolated LH-secreting adenomas are quite rare and less common than FSH- and/or combined FSH- and LH- secreting adenomas.

We report an 18-year old woman who presented with galactorrhea and amenorrhea of 6 months' duration. Previous menses were regular, but hirsutism was noted since the age of 10 years. Visual fields were normal. A CT scan demonstrated a homogeneously enhanced 2.0 cm intrasellar mass with suprasellar extension. Serum LH and FSH values were within normal limits (see Table), while the serum α′-subunit concentration was 12.9 ng/ml (nl. < 2.5 ng/ml). Serum prolactin

LH-Secreting Adenoma Presenting with Galactorrhea-Amenorrhea in an 18-Year-Old Woman *(continued)*

(PRL) ranged from 46–76 ng/ml with an increase to 121 ng/ml at 30 minutes following injection of 500 µg TRH i.v. Serum androgens were normal and sonography of the pelvis revealed normal-sized multifollicular ovaries. She was treated for 6 months with 2.5 mg bromocriptine b.i.d. with no change in the size of the pituitary mass demonstrable on CT scan. Serum PRL levels normalized (see Table) with resumption of menses at intervals of 45 days. Following transsphenoidal adenomectomy regular menses have been interspersed with episodes of oligomenorrhea. Her mean postoperative serum PRL, LH and FSH levels have been in the normal range, and the α-subunit concentration was 0.05 ng/ml. Immunoperoxidase staining of the adenoma showed convincing staining with anti-LH-beta.

Mean + SEM Levels of Serum LH, FSH and PRL

	n	LH (IU/L)	FSH (IU/L)	PRL (ng/ml)
Pre-treatment	4	9.9 ± 4.9	12.5 ± 3.4	65.4 ± 5.7
Bromocr. treatment	3	29.9 ± 13.2	17.2 ± 2.0	13.8 ± 1.0
Post-operative	8	14.1 ± 3.1	8.0 ± 2.1	14.5 ± 2.6

The data do not exclude a possible mixed tumor in which PRL cells regressed after bromocriptine treatment, thereby causing an absence of immunoperoxidase staining for PRL. Normal levels of serum LH and FSH may be associated with a gonadotropin secreting pituitary adenoma and determination of the serum α-subunit concentraton is of value in suggesting the diagnosis.

Plasma LH Pulsatility in Female Hypogonadal Mice with Preoptic Area Transplants Marie J. Gibson, Gregory M. Miller, Derrick Hodge, and Ann-Judith Silverman, Division of Endocrinology, Box 1055, Mount Sinai School of Medicine.

Preoptic area (POA) brain grafts containing GnRH cells correct many reproductive deficits in mutant hypogonadal (hpg) mice. Hpg females with IIIrd ventricular implants may show reflex ovulation with increased plasma LH within 10 min of mating. Progesterone challenge stimulates an LH surge and ovulation in a portion of those treated and spontaneous ovarian cyclicity is observed (rarely) following pregnancy.

Although it is widely accepted that pulsatile LH secretion, reflecting pulsatile stimulation by GnRH, is a basis of normal reproductive function, there are no studies of such pulsatility in any female mice. This is an initial study describing such pulsatility both in normal and in hpg female mice bearing POA grafts. Normal mice ovariectomized at 3-months-old and hpg mice ovariectomized 4 months after graft surgery were studied 3 wks after ovariectomy. Blood samples (0.1cc) were obtained via intrajugular cannulas from awake animals at 10 min intervals for 4 h. Resuspended red blood cells were returned after each sample. RIA of LH was performed on plasma duplicates (25 µl).

Group	N	Ovarian Wt. (mg)	Plasma LH (ng/ml)	# Pulse/h	Pulse Amplitude (ngLH)
Normal	6	8.3 ± 1.1	1.08 ± 0.25**	0.96 ± 0.16*	1.06 ± 0.53
HPG/POA	9	8.4 ± 1.4	0.49 ± 0.09	0.69 ± 0.10	0.45 ± 0.15
HPG/POA	4	7.6 ± 2.7	0.35 ± 0.03	—	—

:pulses present; :no pulses; *p < 0.05, **p < 0.02 vs. HPG/POA

Ovarian weights in hpg mice with POA grafts were in the normal range (vs. <1.0 mg if untreated). LH pulsatility was evident in all normal and in 9/13 hpg mice. Mean plasma LH levels and number of pulses/h were significantly lower in hpg females, but there was not a significant difference in pulse amplitude due to the high variation in normal values. Individual hpg mice had measures in the normal range (eg. #G60 with 1.25 pulse/h, mean plasma LH: 0.98ng/ml, and 0.81 pulse amplitude).

Evaluation of neuroanatomical connectivity to grafts that did and did not support detectable LH pulsatility is in progress. Integration of transplanted GnRH neurons into host hpg brain provides an excellent model for the study of neuroendocrine function.

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Regulation of the Glucose Transporter and Its mRNA by Thyroid Hormone in ARL 15 Cells Steven P. Weinstein, Julie Watts, Peter N. Graves, and Richard S. Haber, Division of Endocrinology, Box 1055, Mount Sinai School of Medicine.

We have studied the regulation of the glucose transporter by thyroid hormone in ARL 15 cells, a thyroid hormone-responsive cell line derived from rat liver. T_3 treatment (50 nM for 48 hours) of confluent cell monolayers grown in thyroid hormone-deficient medium increased the rate of uptake of $[^3H]$2-deoxyglucose by 2.3-fold; this effect was half-maximal at a T_3 concentration of 5 nM. The uptake of the non-metabolizable hexose $[^3H]$3-O-methylglucose was comparably increased, confirming a stimulation of glucose transport by thyroid hormone in these cells.

Because depletion of medium glucose has been shown to cause an adaptive increase in glucose transporters in other cell lines, the possibility that the above effects of T_3 might reflect an adaptation to relative glucose deprivation was investigated. After 48 hours of T_3 treatment (with daily medium changes) glucose concentrations in the medium of T_3-treated monolayers were indeed significantly lower than in controls, falling from an initial level of 1 g/l to from 0.2 to 0.5 g/l. We therefore repeated the measurements of the effects of T_3 on $[^3H]$2-deoxyglucose uptake in high-glucose (3.7 g/l) medium. T_3 caused an increase in $[^3H]$2-deoxyglucose uptake that was virtually identical to that observed in low-glucose (1 g/l) medium, indicating that glucose depletion did not play a significant role in our observations.

To elucidate the mechanism of the stimulation of the glucose transporter by T_3, the number of glucose transporter units in crude membrane preparations was quantitated by measuring the glucose-inhibitable binding of $[^3H]$cytochalasin B. The K_D for specific (glucose-inhibitable) binding of $[^3H]$cytochalasin B was about 50–60 nM. T_3 treatment caused a 2.5-fold increase in the glucose-inhibitable binding of this ligand (at non-saturating concentrations) that was nearly identical in magnitude to the stimulation of $[^3H]$2-deoxyglucose uptake. Since the affinity of the glucose transporter for cytochalasin B as estimated from its inhibition of $[^3H]$2-deoxyglucose uptake was found to be unchanged by T_3 treatment, it can be inferred that T_3 causes an increase in the number of glucose transporter units.

Northern blot analysis of total cellular RNA using a cDNA probe for the rat brain glucose transporter showed a strong 2.9-kilobase hybridization signal after stringent washing, indicating that ARL 15 cells express the specific mRNA for this type of glucose transporter. T_3 treatment rapidly (within hours) increased the abundance of this mRNA, assessed by densitometry, to four times the basal level.

It is concluded that thyroid hormone increases glucose transport, the number of glucose transporter units, and the abundance of glucose transporter mRNA in ARL 15 cells. Thyroid hormone may thus be a regulator of the glucose transporter gene.

A New Thyroglobulin Gene Product? Rat Thyrocytes Contain High Levels of Two Thyroglobulin mRNA Species P. N. Graves and T. F. Davies, Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

Thyroglobulin (Tg) is one of the major immune targets in autoimmune thyroid disease. Our 1B-6 clone of FRTL-5 rat thyroid cells has proven a useful, and well-defined, model for the study of antigen presentation to the immune system and we have previously reported the regulation of their Tg mRNA by cytokines. However, using oligonucleotide probes to the 5′ region of the rat Tg gene in proliferating 1B-6 cells and stringent hybridization conditions we recognized not just a 9.0 kb mRNA (rTg-1) known to encode the 330 Kd Tg subunit, but a single additional mRNA of about 1.1 kb (rTg-2) not previously described. Whereas both an Exon 1 and an Exon 2 probe detected both species of mRNA, a probe to the 3′ end of the known rat Tg mRNA sequence only detected rTg-1. Further analysis demonstrated that rTg-2 mRNA was present in the cytoplasmic fraction of lysed 1B-6 cells and was polyadenylated. In contrast to rTg-1 mRNA, the level of rTg-2 mRNA rapidly declined when TSH was removed from the culture medium and rapidly increased upon its readdition. Cultured thyrocytes from the parent FRTL-5 and FRTL cell lines, as well as the Wistar rat derived WRT cell, also contained high levels of both Tg mRNAs. Furthermore, rTg-2 was easily detectable in total RNA derived from the intact thyroid glands of TSH-treated Fisher and Buffalo rats.

A New Thyroglobulin Gene Product? Rat Thyrocytes Contain High Levels of Two Thyroglobulin mRNA Species *(continued)*

Since the Exon 1 probe lies within that portion of Tg mRNA encoding the signal peptide, a polypeptide product of the small Tg mRNA should be an integral membrane or secreted protein. In addition, the Exon 2 probe spanned one of the hormonogenic tyrosines, raising the possibility of a physiological role for such a secreted product. The exceptional size of the Tg gene with its many exons and some very large introns make it a target for mutations leading to splicing errors. However, our consistent finding of high levels of two Tg mRNA species in the rat suggests the normality of their presence. It is likely that the smaller Tg mRNA is the result of alternative splicing and/or utilization of an alternative polyadenylation site. Since the 1.1 kb Tg mRNA has not been previously reported, most likely due to the choice of probes, it will be important to determine the role of a putative polypeptide product from this smaller mRNA species in thyroid function and thyroid autoimmunity.

Strain Specific Determination of Thyroid Cell MHC Class II Antigen Expression—Evaluation of Established Wistar and Fisher Rat Thyroid Cell Lines D. S. Neufeld, P. Graves, M. Platzer, and T. F. Davies, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

The major histocompatibility complex (MHC) genes, primarily of the class II region, are linked to susceptibility to autoimmune thyroid disease in animals and humans. It is also known that the quantity of MHC class II antigens which are expressed on the appropriate cell surface is of vital importance to immune function as well as their quality (ie, haplotype). Recently we provided evidence that not only are different MHC antigens variably effective at protecting a species from autoimmune thyroid disease but that they exhibit similar variability in the extent of their MHC class II antigen expression at the level of the thyroid epithelial cell (Endocrinology 124:1754, 1989). Such studies examined primary Buffalo and Fisher rat thyroid monolayer preparations which are inevitably heterogeneous and in which it is difficult to exclude non-thyroid cell influences.

We have, therefore, taken the opportunity of comparing the newly available Wistar (thyroiditis susceptible) rat thyroid (WRT) cell line with a cloned cell (1B-6) derived from the Fisher (thyroiditis resistant) rat thyroid cell line (FRTL-5). There was no detectable constitutive MHC class II antigen or RT1.D alpha chain mRNA expression in either WRT or 1B-6 cells. Cultures of both cells expressed MHC class II gene induction in response to recombinant rat gamma interferon (IF). After 72 hours of exposure to 25 U/ml gamma IF there were over 80% of WRT cells expressing class II antigen, detected by flow cytometric assessment, compared to only 15% of 1B-6 cells. This earlier and greater expression of MHC class II antigen was reflected in the alpha chain mRNA responses with peak levels in WRT cells after only 24 hours of gamma IF, a time when 1B-6 cells show minor increases in mRNA. To examine whether this observation was thyroid-cell specific we developed pulmonary fibroblast lines from Wistar and Fisher rats and observed a similar difference in gamma IF susceptibility.

Hence, rat strains resistant to autoimmune thyroid disease exhibit a fundamental difference in their MHC class II gene responsiveness to cytokines which may contribute to their disease susceptibility profiles.

Effect of Sex Steroids on Human Prostatic Fibroblasts in Tissue Culture A. Levine, M.D., E. Diamond, Ph.D., J. L. Gabrilove, M.D., and A. Kirschenbaum, M.D., Division of Endocrinology and Department of Urology, Mount Sinai Medical Center, New York, NY.

Androgen deprivation has been shown to cause involution of prostatic epithelial cells in men with benign prostatic hypertrophy (BPH). Al-

Effect of Sex Steroids on Human Prostatic Fibroblasts in Tissue Culture *(continued)*

though prostatic stromal cells play a key role in BPH, the effect of sex steroids on prostatic fibroblasts has not been established. Prostatic tissue obtained during suprapubic prostatectomy for BPH was incubated for 48 hours at 37°C, 5% CO2 with 0.15% collagenase. After washing and centrifugation the final pellet was brought up in Ham's F10 supplemented with NaHCO3, glucose, insulin and 10% Fetal Calf Serum (FCS) and plated in 25 cm2 flasks. After 6 passages, cells were determined to be fibroblasts visually and via positive staining for vimentin and negative staining for cytokeratins and desmin.

All experiments were done in duplicate and repeated at least 4 times. Cells were grown in Ham's F10 + 10% charcoal treated FBS (Stripped-sFBS) with and without dihydrotestosterone (DHT) 10^{-9} M and estradiol (E2) 10^{-11} M. Cells were counted in a hemocytometer after 2 weeks incubation.

DHT 10^{-9} M caused an increased proliferation of fibroblasts over control cells which was statistically significant (p less than 0.5). The addition of E2 10^{-11} M to the DHT treated cells obliterated the effect of DHT on proliferation. E2 alone did not have any effect on proliferation. The fibroblasts were stained for the presence of E2 receptors using a monoclonal Ab-ABC-peroxidase technique (Abbott Labs) and no E2 receptors were detected.

We conclude that DHT at physiologic concentrations causes an increase in human prostatic fibroblasts in vitro. E2 obliterates this effect of DHT. As there were no E2 receptors detectable on these fibroblasts, the E2 may be acting as a competitive inhibitor of DHT at the level of the androgen receptor.

HIV Counselling and Testing in New York City Chest Clinics J. J. Adler, D. Ruggiero, T. Davis, D. Guishard, C. Larkin, New York City Department of Health, NY

In response to CDC recommendations that tuberculosis (TB) infected and diseased persons be tested for HIV infection, New York City has initiated confidential, nonmandatory counselling and testing in its chest clinics citywide.

Chest clinic nurses were trained by Health Department HIV counselors in pre and post-test counselling techniques. TB training was provided to HIV counselors, and HIV+ individuals are encouraged to attend chest clinics for tuberculin skin testing. Educational materials have been developed, and a confidential record keeping system has been established. Referral is provided for additional psychosocial and medical services when necessary.

Intense monitoring of those dually (HIV/TB) infected/diseased includes follow-up with one year of INH prophylaxis for infected and extended chemotherapy for diseased patients.

	Counselled	Tested	HIV+
		%	%
TB Diseased	15	12 (80.0)	8 (66.6)
TB Infected	770	248 (32.2)	20 (8.1)
Total	785	260 (33.1)	28 (10.8)

Preliminary results as of October 1988 indicate a higher rate of acceptance of HIV testing and seropositivity among those with tuberculosis disease than those with only tuberculous infection.

Sensitive Thyroid Autoantibody Assays Accurately Predict Susceptibility to Postpartum Thyroiditis A. Stagnaro-Green, R. Cobin, E. El-Harazy, and S. H. Roman, Division of Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Postpartum thyroid disease (PPTD) in New York City has been reported as uncommon, with an incidence below 2% (Arch Int Med 146:1361, 1986). As part of the first prospective study of PPTD in the USA we screened 388 women in the first trimester of pregnancy using routine thyroid function tests including specific and sensitive ELISAs for thyroid autoantibodies (anti-TPO & anti-Tg). 18.6% of women screened had one or both thyroid autoantibodies (mean ± SEM anti-TPO ELISA Index = 0.44 ± 0.43, anti-Tg = 0.42 ± 0.40, normal <0.2). To date 57 women (28 antibody positive and 29 antibody negative matched for age and race) have been successfully followed to 6 months postpartum from an initial study group of 65 women who agreed to participate (88% follow up). Each subject entered into the study was monitored for peripheral blood T cell subset changes and HLA serotyped.

Thyroid autoantibody titers were suppressed during pregnancy in 23/28 (82%) and 5 of these 23 (22%) antibody positive women developed thyroid dysfunction 3–6 months postpartum. The CD4:4B4/CD4:2H4 ratio decreased at the time of onset of PPTD. Four of the 5 (80%) women who developed postpartum thyroiditis were HLA-DR3 (compared to a total of 12/57). There was no relationship between the onset of thyroiditis and autoantibody immunoglobulin G subclass with IgG1, IgG2, and IgG4 being equally distributed in the affected and unaffected subjects.

Hence, the overall incidence of postpartum thyroiditis in New York City, by extrapolation, is approximately 4% and the presence of thyroid autoantibodies is a major risk factor for the disorder. In addition, suppression of TSH, assessed by sensitive immunoradiometric assay, was the most useful initial observation in women with PPTD. These data emphasize the increased risk of thyroid autoantibody positive women developing PPTD, define the utility of a sensitive TSH assay as the initial marker for PPTD, and clarify the incidence of PPTD in New York City.

Decreased IL-2 Synthesis in Insulin-Dependent Diabetics Is Regulated at the mRNA Level Usha Jain and Karen S. Zier, Division of Endocrinology, Mount Sinai Medical Center, New York, NY.

The immune system is designed to recognize foreign invaders and to eliminate them from the body via the humoral or cell mediated system. Upon occasion, however, this mechanism can turn against itself and initiate an attack against self components. Such pathological states are referred to as autoimmune diseases. Insulin dependent diabetes (IDD) is an example of an autoimmune disease in which the target organ is the insulin producing beta cells in the Islets of Langerhans. Recent results suggest that T cells are the primary effector cells in beta cell destruction. We previously reported one of the few generalized abnormalities affecting the human IDDs T cells which is not secondary to poor metabolic control, namely the decreased synthesis of Interleukin-2 (IL-2) following stimulation with PHA. IL-2 is a hormone-like growth factor which mediates effective interaction between cellular subsets within the immune system and influences T cell proliferation. Since these results were obtained on the cellular level, we turned to molecular techniques to define the underlying basis for the IL-2 defect.

The results of our experiments indicated that the decreased levels of IL-2 contained in supernatants from diabetic T cells following stimulation with PHA were associated with decreased steady state levels of mRNA. Kinetics studies demonstrated that a difference in IL-2 mRNA accumulation between IDDs and age-matched controls could be observed by 6 hours after stimulation. Furthermore, low levels of IL-2 also were generated when the activation signals bypassed the T cell receptor, by using the calcium ionophore, A23187 and the phorbol ester, PMA.

These results suggest that the IL-2 defect in IDDs is due to an abnormality in the regulation of the expression of the IL-2 gene. Future experiments will be directed towards defining the underlying mechanisms(s).

Gastroenterology

Octreotide Treatment of Carcinoid Hypertensive Crisis Richard R. P. Warner, M.D., Joseph Profeta, M.D., Erno Grunstein, M.D., and Sridhar Mani, Division of Gastroenterology, Department of Medicine and Department of Anesthesiology, The Mount Sinai School of Medicine, New York, NY.

Octreotide Treatment of Carcinoid Hypertensive Crisis ***(continued)***

The typical hemodynamic changes of carcinoid crisis, hypotension, and even shock usually are effectively inhibited by octreotide. A few carcinoid syndrome (CS) patients have hypertension which severely increases during such a crisis. We report the response to octreotide in such an instance.

This 62-year-old white female CS patient had 1–2 years of flushing, diarrhea, weight loss, 24-hour urine 5-HIAA of 90 mg, and enlarged liver with metastatic carcinoid demonstrated on needle biopsy. The primary site was not found. Past history included a benign thyroid nodule, peptic ulcer disease and hypertension treated with hydrochlorothiazide and triamterene for the past 7 years (BP 170/90). Urinary catecholamines were normal. She was hospitalized for percutaneous hepatic artery infusion treatment. In spite of p.o. diazepam and diphenhydramine premedication, she arrived at the radiology department in a carcinoid crisis with marked flushing, BP 240/130 and VR 120. IV methotrimeprazine and hydrocortisone rapidly corrected the hypertension but VR rose to 160. After IV propranolol and fentanyl, flush, heart rate and BP improved (160/80). The catheterization was abandoned. Two months later, after premedication with larger doses of diazepam and diphenhydramine, she again arrived at the radiology department in a carcinoid crisis with marked flushing and hypertension (230/120) but no tachycardia. After 10 minutes of multiple injections of methotrimeprazine (14 mg) and diazepam (10 mg), BP and flush receded. 30 minutes later BP rose again to 210/110 accompanied by flushing. IV octreotide was given, a 5 mcg bolus and then 95 mcg over 30 minutes. BP declined to 180/90 and flush cleared within the first 15 minutes and remained stabilized at lower levels for the next 2 hours. Hepatic artery catheterization, chemotherapy and emboli injection were successfully done.

The rare occurrence of hypertension in a CS crisis has been observed previously. We observed the prompt correction of hypertension during such a crisis when treated with IV octreotide. It appears that the severe hemodynamic changes of carcinoid crisis, both hyper and hypotensive, response to octreotide. This somatostatin analog should be available for emergency use in all CS patients.

Benign and Malignant Strictures in Ulcerative Colitis Vivek Gumaste, DB Sachar, A. Greenstein, Div. of Gastroenterology, City Hospital Center at Elmhurst, NY.

Colorectal strictures in ulcerative colitis may be benign or malignant. A retrospective study of the medical records of 1156 patients with ulcerative colitis admitted to The Mount Sinai Hospital between 1959 and 1983 was undertaken to compare benign and malignant strictures with regard to incidence, anatomical distribution, time of occurrence and clinical presentation.

Seventy strictures were identified in 59 (5.1%) of the 1156 patients. Seventeen (24%) of these strictures were malignant, while the remaining 53 (76%) were benign. All the strictures detected before ten years of colitis were benign (12/12); from 10–19 years, 84% were benign (21/24); but at 20 years and over, the majority (61% i.e 14/23) were malignant. In summary 78% of benign lesions were discovered before 20 years while 82% of malignant ones were detected after 20 years of disease ($x^2 = 18.88$, DF = 1, P 0.001). A difference in their anatomical distribution was also noted. In the rectum 10% (4/40) were malignant and in the descending colon and splenic flexure none (0/8). But in the sigmoid colon 47% of the strictures were malignant (7/15); and in the right colon proximal to the splenic flexure 86% were malignant.

The most striking aspect of our study was the difference in presenting symptoms exhibited by the two different groups. All 7 patients who presented with intestinal obstruction had malignant strictures. The 8 patients with constipation were equally distributed. Neither obstruction or constipation was present in 44 patients (6 malignant and 38 benign).

Thus the occurrence of symptomatic intestinal obstruction with a stricture in the presence of ulcerative colitis appears to be pathognomonic of malignancy.

Conclusion: A stricture in ulcerative colitis is more likely to be malignant if it presents with obstruction, occurs after 20 years, or is located proximal to the splenic flexure. In contrast a benign stricture occurs within 10 years and tends to be left-sided in location.

Sialosyl-Tn: A Novel Mucin Antigen Associated with Poor Prognosis in Colorectal Cancer Patients Steven Itzkowitz, M.D., William Kokal, M.D., Sen-itiroh Hakomori, Ph.D., Division of Gastroenterology, Mount Sinai Medical Center.

Although colon cancers typically produce mucin, it is not known whether tumor mucin plays a biological role in cancer cell behavior. To address this issue, we examined by immunohistochemistry the expression of a mucin-associated antigen, sialosyl-Tn, in 128 primary colorectal carcinoma specimens from 137 patients who underwent curative surgical resection, and correlated antigen expression with disease-free and overall five-year survival.

Expression of sialosyl-Tn antigen occurred in 112 (87.5%) tumors, and was independent of age, gender, tumor location, Dukes' stage, depth of invasion, degree of differentiation, and ploidy status. Overall survival for patients with sialosyl-Tn-negative vs. sialosyl-Tn-positive tumors was 100% vs. 73% ($p < 0.05$) and disease-free survival was 94% vs. 73% ($p = 0.12$). Dukes' stage, depth of invasion, and ploidy status each significantly influenced overall survival and within these groups, individuals with antigen-negative tumors did considerably better than those with antigen-positive tumors. Multivariate regression analysis revealed that the two variables of most importance for predicting survival (disease-free and overall survival) were tumor ploidy ($p < 0.001$) and sialosyl-Tn expression ($p < 0.05$).

We conclude that sialosyl-Tn expression is an independent prognostic factor in colon cancer, thereby suggesting a role for mucin in the behavior of these neoplasms.

Treatment of Ulcerative Colitis with Fish Oil Omega-3 Fatty Acid: An Ongoing Open Trial H. D. Janowitz and P. Salomon, Division of Gastroenterology, Box 1069, Mount Sinai Medical Center.

The purpose of this trial is to evaluate the efficacy of omega 3 fatty acid, a leukotriene B4 inhibitor as well as an oxygen free radical scavenger, in the treatment of ulcerative colitis (UC).

An open trial of 9 patients with mild to moderate UC who had either failed or refused conventional therapy was performed using 15 grams of fish oil (Max EPA Sherer) containing 3.2 grams of eicosapentanoeic acid (EPA) in three divided doses daily for eight weeks. Patients were continued on their pretrial medication (if any). The severity of UC before and during the study was graded by prior defined criteria which included but was not limited to: daily stool diaries, sigmoidoscopy at 0, 4 and 8 weeks and clinical response.

Of the nine patients enrolled thus far, five have completed the eight week trial and are currently being maintained on fish oil while two others have completed six weeks of therapy. All tolerated the fish oil and had no alteration in routine blood studies. Seven obtained improvement as measured by the criteria stated above, two patients were without change and none worsened. Steroid dose could be discontinued in one and reduced in another of the three patients on prednisone.

The results to date appear to justify a double-blinded trial of this dietary supplement in ambulatory patients with UC.

Initial Experience with Endoscopic Ultrasonography (EUS) for Upper Gastrointestinal (UGI) Disease. H. Snady, M.D., Ph.D., Division of Gastroenterology, Mt. Sinai Hospital.

EUS allows new sonographic access to the UGI tract and surrounding organs. Because the sonographic probe can be placed adjacent to submucosal and mucosal lesions, and because the sound wave frequencies used are higher than those used for standard extracorporeal sonography, unsurpassed resolution is possible. The information obtained from EUS results in a significant advance in tumor characterization and staging. In this study the feasibility of performing EUS as an outpatient procedure was evaluated, as well as the ability of EUS to provide clinically useful information beyond that available from standard imaging techniques.

Methods: 59 patients (age range: 28–92) were evaluated by EUS in an office setting. Preliminary standard endoscopy was performed at the time of EUS in 22/59 cases. All other patients had had a complete standard endoscopy within the past month. The GF-UM2/EU-M2 endoscopic ultrasound system (GF-UM2) was used for EUS. After topical pharyngeal anesthesia, intravenous medication was administered

Initial Experience with Endoscopic Ultrasonography (EUS) for Upper Gastrointestinal (UGI) Disease *(continued)*

(range: meperidine 0 to 50 mg, with up to diazepam 10 mg and/or midazolam 5 mg).

Results: Diseased organs successfully visualized by EUS were: pancreas-38 of 40, stomach-12 of 13, esophagus-8 of 8, and biliary tract-2 of 2. No complications occurred. Information from EUS, *not* shown by other diagnostic techniques, was obtained in 32/38 patients with pancreatobiliary disease and 19/21 patients with gastroesophageal disease, resulting in an increase in accuracy of diagnosis and/or tumor staging from 47% to 87% for pancreatobiliary disease and from 5% to 79% for esophagogastric disease. EUS findings were confirmed by laparotomy in 29, by biopsy and/or angiography in 13, and by clinical course in 17.

Technical problems encountered were: 1) The GF-UM2 did not pass a) through the pharynx-1 patient, b) into the duodenum-3 patients, c) into the 3rd part of the duodenum-3 patients. 2) Disease extended to areas outside the optimal 1–5 cm focal range-2 patients.

Interpretative problems encountered were: 1) Assignment of a diagnosis to cases where findings are not clearly benign or malignant-3 patients. 2) Demonstration of foci of metastatic tumor in small lymph nodes was not possible-6 patients.

Conclusions: Objectives of the EUS examination were achieved in 86%. EUS represents a significant advance in the evaluation of gastrointestinal tumors. Preliminary standard endoscopy facilitated entering the duodenum, which is required for complete evaluation of the pancreas and adjacent vessels. EUS can be successfully performed in an office setting.

Endoscopic Ultrasonography (EUS) Compared to Computerized Tomography (CT) for Preoperative Staging and Assessment of Resectability of a Pancreatic Adenocarcinoma or Mass H. Snady, M.D., Division of Gastroenterology, Mt. Sinai Hospital.

Selection of a management plan for pancreatic carcinoma requires exact knowledge of tumor stage. Pre-operative assessment of a potentially resectable pancreatic mass by CT is widely used, but often of limited value, especially for lesions which appear to be less than 5 cm.

Methods: 16 patients (6 female, 10 male) with a pancreatic mass less than 5 cm were to undergo surgical treatment for continued symptoms and/or possible resection of malignant disease. EUS and CT were used for staging according to the TNM staging classification of the American Joint Committee on Cancer (AJCC). EUS was performed using the Olympus GF-UM2 7.5 MH system.

Results: Disease was resectable in 10 (5 malignant, 5 benign); all underwent variations of pylorus preserving resection and pancreatic drainage. Disease was not resectable in 6 (5 malignant underwent biliary and gastric bypass; 1 benign underwent gastric bypass). Thirty-day mortality was 1/16 from uncontrollable hypercalcemia in a patient with metastatic disease not detected by any preoperative tests.

Preoperative Assessment of Resectability

	Accuracy	True positive	True negative	False positive	False negative
EUS	88%	9	5	1	1
CT	56%	8	1	5	2

For CT, 6/7 errors were in assessing venous involvement.

AJCC Staging Agreement with Surgical Pathology

	Correct	Overstaged	Understaged	Not Staged
EUS	56%	1/16	5/16	1/16
CT	12%	3/16	8/16	3/16

Staging errors included: a) undetected micrometastases less than 1 cm to liver (EUS-#1, CT-#1), to regional modes (EUS-#3, CT-#4); b) misinterpreted involvement of portal, mesenteric or splenic veins (EUS-#0, CT-#4); c) incorrect assessment of primary lesion (EUS-#3, CT-#5).

Conclusions: In this small series, EUS was more accurate than CT in the assessment of cancer invasion and prediction of resectability. EUS represents a significant advance in pancreatic tumor staging.

General Medicine

Correlates of the Pressor Response to the Clinic in Hypertensives with and without Diabetes Fernando Elijovich, MD and Cheryl L. Laffer, MD, PhD, Division of General Medicne, Box 1087, Mount Sinai Medical Center.

We studied the pressor response to the clinic visit (PCR) in 17 essential hypertensives with (DD) and 34 without (NO) diabetes. They had ambulatory blood pressure (BP) monitoring after 4 wks off therapy. Systolic (S), diastolic (D), mean (M) and heart rate (HR) responses were calculated as the differences between awake, clinic-related and clinic-unrelated BP readings. NO and DD did not differ in age, duration of hypertension (DUR), body mass index, HR, PRA or target organ damage.

BP was 161 ± 4/101 ± 1 mmHg in NO and 178 ± 5/103 ± 1 in DD, $p < 0.01$ for systolic. PRC of NO was 14 ± 2/9 ± 1 and that of DD 12 ± 4/7 ± 2, ns. PRC of NO (S, D or M) showed a normal distribution while that of DD was bimodal with one peak in the depressor range. The % of patients with D depressor responses was: NO 6% and DD 24%, $0.1 > p > 0.05$. HR responses were -3 ± 2 bpm in NO and 3 ± 2 in DD, $p = 0.05$. Clinic-related decreases in HR were seen in 59% of NO and 29% of DD, $p < 0.05$. Patients' sex had no effect on PRC. Race had an effect in NO only; no Hispanics (H) vs 43% of Blacks had depressor responses, $p < 0.001$. In NO, D responses showed a negative correlation with DUR, $r = -0.40$, $p < 0.02$. In DD, S responses correlated with age, $r = 0.50$, $p < 0.05$, while D showed negative correlations with fasting blood sugar (FBS), $r = -0.48$, $p = 0.05$, BP, $r = -0.53$, $p < 0.03$ and weight (WT), $r = -0.56$, $p < 0.02$. Stepwise regression analysis explained 19% of the variability of M responses in NO, $F = 3.6$, $p < 0.04$. DUR and a dummy for race ($B = 0$, $H = 1$), were the only significant regressors ($M = 9.5 - 0.3\ \mathrm{DUR} + 5.7\ \mathrm{RACE}$). In contrast, 64% of the variability of M was explained in DD, $F = 4.0$, $p < 0.03$, ($M = 91 + 0.3\ \mathrm{AGE} - 0.02\ \mathrm{FBS} - 0.17\ \mathrm{WT} - 0.47\ \mathrm{BP} - 10\ \mathrm{RACE}$).

In summary, PRC of NO is: a) consistently pressor in H while frequently depressor in B, b) attenuated by long duration of hypertension, and c) poorly predicted by clinical characteristics. In contrast, PRC of DD is: a) frequently depressor (independent of race), b) associated with increases in HR, and c) largely explained by a combination of variables (age and blunting of the response with more severe BP, worse FBS and excess body weight). We conclude that: 1. the poor predictability of PRC in NO is consistent with its reported poor reproducibility, and 2. the relationship between factors associated with autonomic dysfunction and blunting of PRC in DD is consistent with mediation of PRC by autonomic stimulation.

Infectious Diseases

Thoracic Isolation of *Aspergillus* in the AIDS Population A Klapholz, W. Talavera, D. Perlman, P. Villamena, B. S. Saltzman, S. Yancovitz. Beth Israel Medical Center, New York, NY.

Invasive aspergillosis (IA) has been associated with corticosteroid (CS) therapy and granulocytopenia in non-AIDS immunocompromised patients (pts.). The role of *Aspergillus* spp. (AS) as a pathogen in AIDS has not been clearly defined. We undertook a retrospective review to determine the clinical spectrum of pulmonary aspergillosis (PA) in AIDS and to elucidate the risk factors for PA.

From 1984–1988 over 1500 AIDS patients were seen at Beth Israel Medical Center. Thoracic isolation of AS was found in nine. Clinical PA was diagnosed in seven. All were gay men. At presentation, all 7 had fever, 5 cough, 3 dyspnea, and 2 pleuritic chest pain. CXR revealed bilateral infiltrates (BI) in 4, BI and cavitation in 2, and cavitation alone in 1. Predisposing conditions included CS therapy in 5, granulocyte count <2000 in 5, granulocytopenia and CS in 2, broad spectrum antibiotics (6), alcoholism (2), and renal failure (1). AS was initially identified antemortem in all 9; cytologically in bronchoalveolar lavage (BAL) in 3, transbronchial biopsy in 5, BAL and transthora-

Thoracic Isolation of *Aspergillus* in the AIDS Population *(continued)*

cic needle aspirate (1), open lung biopsy (1), and postmortem in 1. Six of seven had at least one concomitant pulmonary process: PCP (4), Kaposi sarcoma (2), CMV (2), Nocardia (1), Cryptococcus (1), MAI (3). Eight of nine patients with AS identified antemortem received Ampho B. 2 had radiographic improvement (one alive receiving therapy, one died of other causes without necropsy). Three who had no improvement and died, underwent necropsy. IA was documented in 2/3, each of whom had previously received CS. The third who had AS seen on BAL but did not have confirmation of IA at necropsy had not received CS and was never granulocytopenic. Necropsy findings showed: lung and mediastinal lymph node involvement (1), dissemination (2).

Clinical PA is uncommon in AIDS. When AS is diagnosed in the setting of CS therapy or granulocytopenia, one must suspect invasive disease.

Absence of Hematologic Toxicity of Zidovudine in HIV-Infected Patients without AIDS Gerald Pierone, M.D., Janet Lin, M.D., Ananthram Pottipati, M.D., Glenn Turett, M.D., Joseph R. Masci, M.D., Peter Nicholas, M.D., Department of Infectious Diseases, Mt. Sinai Services, Elmhurst Hospital Center, Elmhurst, NY.

Zidovudine (Zd) therapy is associated with a high incidence of hematologic toxicity in patients (pts) with AIDS. Anemia, often necessitating dose reduction and blood transfusion is common. Many pts infected with HIV, but not meeting the surveillance definition of AIDS, are receiving Zd in clinical trials or uncontrolled fashion. We sought to determine the incidence of hematologic toxicity caused by Zd in HIV-infected pts without AIDS.

Records of 15 HIV-positive, non-AIDS pts begun on full-dose Zd (1200 mg/d) before 1/1/89 were reviewed. Two pts were excluded, one due to non-compliance and one with dose reduction due to GI distress. Thirteen pts were treated for at least 3 consecutive months (ave. 7.9; range 3–14.5 mo). Initial CD4 lymphocyte counts averaged 181/mm3 (range 16–447). No pt required dose reduction or blood transfusion. The mean (±1 SD) initial hemoglobin level was 13.7 (±1.9) mg/dl compared to 13.1 (±1.9) mg/dl at the end of the follow-up period. The mean initial WBC count was 5600 (±2030)/mm3, declining to 5000 (±1780)/mm3. Neither change was significant ($p > 0.1$) by paired t-test.

We conclude that Zd is not associated with clinically significant hematologic toxicity in HIV-infected non-AIDS pts.

Prospective Study of Indium^{111} Leukocyte Scanning for the Diagnosis of Focal Infection: Clinical/Imaging/Microbiologic Correlations Burt R. Meyers, M.D., Alejandra C. Gurtman, M.D., Meryl H. Mendelson, M.D., Michelle Halpern, M.D., Janet Lin, M.D., Yosef Morad, M.D., Christopher Palestro, M.D. and Shalom Z. Hirschman, M.D., Division of Infectious Diseases and Nuclear Medicine, The Mount Sinai Hospital.

Eighty-one patients who had indium scanning to rule out focal infection from 10/88 to 4/89 were studied prospectively. The most common indications for indium scanning included abscess (25), osteomyelitis (23), FUO (9), septic source (7). 83% had fever, 55% WBC greater than 10,00/mm^3; 80% greater than 60% PMNs. 27% underwent ultrasonography (US), 31% CT scan, and 25% bone scan (BS). A final diagnosis of infection (clinical/microbiologic) was documented in 59 (45 focal). 45/81 indium scans were positive for focal infection (34 true positive); 35 negative for focal infection (26 true negative). False positive indium scans were due to a neoplasm in 5/11. False negative indium scans (N = 10) included 3 pyelonephritis, 2 pneumonia, 2 abscess, 2 skin/soft tissue, 1 osteomyelitis. 9/22 patients who had ultrasonography and indium scanning had a final diagnosis of focal infection; 5/9 were ultrasonography positive, 5/9 indium scan positive. 9/25 who had CT scan and indium scan had a final diagnosis of focal infection; 9/9 CT scan positive, 8/9 indium scan positive. 17/20 focal infections, who had bone scan and indium scan, had a final diagnosis of focal infection; 14/17 bone scan positive, 14/17 indium scan positive. Comparative sensitivities and specificities were:

	US	IS	CT	IS	BS	IS
Sensitivity (%)	71	62	100	89	93	82
Specificity (%)	93	100	100	93	100	100

Prospective Study of Indium^{111} Leukocyte Scanning for the Diagnosis of Focal Infection: Clinical/Imaging/Microbiologic Correlations *(continued)*

In conclusion: indium scanning was comparable in sensitivity and specificity with ultrasonography, CT scan and bone scan. Indium scanning for diagnostic work-up of focal infection had an overall sensitivity of 75%, specificity of 70% and predictive value of 75%.

Pyrimethamine-Sulfadiazine in the Prophylaxis of *Pneumocystis carinii* Pneumonia in AIDS Patients with Cerebral Toxoplasmosis Gerald Pierone Jr., M.D., Glenn Turett, M.D., Joseph Masci, M.D., Peter Nicholas, M.D., Division of Infectious Diseases, Mount Sinai Services, Elmhurst Hospital Center.

Objective. To determine if maintenance therapy with sulfadiazine-pyrimethamine (SP) in patients with central nervous system toxoplasmosis (TOXO) and the acquired immunodeficiency syndrome (AIDS) is effective in the prophylaxis of *Pneumocystis carinii* pneumonia or if such patients require additional preventive therapy.

Methods. We reviewed the records of patients maintained on SP following an initial episode of TOXO. The diagnosis of TOXO was established by the presence of typical ring-enhancing lesions on brain CT scan and clinical and radiographic response to therapy with SP in patients at high-risk for HIV infection.

Results. 20 patients who had received at least 3 months of SP, including 3 who had had previous or coincident PCP, were identified. The dosage of sulfadiazine ranged from 2–6 grams per day, pyrimethamine 25–50 mg per day. Zidovudine was also administered to 6 patients (35 patient-months). During 162 patients months of followup, none of the patients developed PCP (mean 8.1 months, range 3–20 months).

Conclusion. Maintenance therapy with SP provides effective prophylaxis of PCP in patients with AIDS.

Zidovudine Prophylaxis for Persons with Accidental Percutaneous Blood Exposure: A Decision Analysis David N. Rose, M.D., Henry S. Sacks, PhD, MD, Divisions of General Medicine and Infectious Disease, Mount Sinai School of Medicine.

Objective. To determine the thresholds of safety and effectiveness which would justify short-term zidovudine (AZT) administration for persons with accidental percutaneous exposure to either HIV-positive blood or blood of unknown HIV-serologic status.

Methods. We used a Markov model to accommodate the short-term risks of HIV infection and AZT effectiveness and toxicity and the long-term risks of AIDS development and mortality. The outcomes studied were life expectancy and lives saved per cohort. Published data were used to estimate seroconversion rate (0.42%), rate of HIV-infected developing AIDS (5%/year), and AIDS survival (50%/year). No information is available on AZT effectiveness and little is known about AZT irreversible toxicity (1 known death among approximately 15,000 recipients). To model the timing of initiation of AZT preventive therapy, we used animal model studies of AZT for the prevention of retrovirus infection, which showed AZT to be 50% effective when first administered three days after viral challenge. Wide variations in all assumptions were made in the sensitivity analysis.

Results. For those with exposure to blood known to be HIV seropositive, the benefits of AZT outweigh the risks under all but a combination of the most skeptical assumptions of AZT safety and effectiveness. Using moderate assumptions (AZT effectiveness 50%, safety 1 death per 15,000 AZT recipients), AZT use averts 174 deaths per 100,000 persons exposed. AZT effectiveness must be greater than 2.6% to justify taking it. If AZT fatal toxicity were as high as 3/15,000, AZT must be greater than 7.8% effective to justify taking it. Wide variations in the assumptions have little effect on the thresholds, with the exception of the likelihood of seroconversion after exposure: If the blood serologic status is unknown, the likelihood of seroconversion is a function of the local prevalence of HIV infection; the AZT benefits do not clearly outweight the risks when the prevalence is below 10%. The risk/benefit ratios remain favorable even if AZT is first initiated 3 days after exposure.

Conclusions. Until the results of clinical trials are known, the decision must be based on strength of belief regarding AZT effectiveness

Zidovudine Prophylaxis for Persons with Accidental Percutaneous Blood Exposure: A Decision Analysis ***(continued)***

and toxicity. Unless studies show AZT to be both highly ineffective and toxic, the benefits of short-term AZT outweight risks after exposure to HIV-positive blood. AZT benefits do not clearly outweight risks after exposure to blood of unknown serologic status.

Liver

Immunohistochemical Characteristics of Bile-Ductlike (Oval) Cells Proliferating During Chemical Hepatocarcinogensis MH Liu, T Han, R Lenzi, PA Slott, and N. Tavoloni, Division of Hematology, Department of Medicine, Mount Sinai Medical Center, New York, NY.

The nature of oval cells proliferating during chemical hepatocarcinogenesis and their role in the emergence of hepatocellular carcinoma are controversial. To shed light on these issues, male Sprague-Dawley rats (100–150 g) were placed on a choline-devoid diet containing 0.05% ethionine (CDE) and hepatic histology and immunohistochemical staining for albumin, vimentin, desmin, and cytokeratin (CK) #7, 8, 18, and 19 were studied using the ABC procedure in formalin-fixed (albumin) or frozen liver sections at 1, 2, 4, 8, 16, 24, 32, and 40 wks of CDE diet. In normal rat liver, albumin is present in hepatocytes; vimentin in endothelial cells, fibroblasts, Kupffer cells, macrophages, and fat-storing cells; desmin in muscle and fat-storing cells; CK-7 and CK-19 in bile duct cells; and CK-8 and CK-18 in both biliary epithelial cells and hepatocytes.

Histologically, oval cell proliferation first became visible in portal tracts at 1 wk of CDE feeding and was massive at 8–24 wks. Cholangiomas were rare and seen at 20–40 wks, while hepatocyte nodules became abundant after 28 wks. Preneoplastic and neoplastic hepatocytes were positive for albumin and CK-8 and CK-18, but not for desmin, vimentin, and CK-7 and CK-19. Oval cells were also negative for desmin and vimentin, and most of them (>95%) displayed no immunoreactivity for albumin. However, all histologically identifiable oval cells, whether or not forming ductlike structures and present in connective or parenchymal tissue, were positive for CK-7, CK-19, CK-8 and CK-18. At 1 wk of CDE diet, CK-7 and CK-19 staining was observed in extant bile ducts and in apparently isolated oval cells located in portal tracts. Cholangiomas, including hyperplastic and dysplastic bile-ductlike structures, were also positive for CK-7 and CK-19 (and for CK-8 and CK-18).

These results indicate that oval cells proliferating during CDE feeding belong to the bile duct lineage. Although their origin is unclear, our results suggest the existence of dormant (embryonic) bile-ductlike cells in portal areas, resurging following carcinogenic insult.

Stabilization and Maintenance of Cytochrome P-450 IIE1 in Primary Hepatocyte Culture by 4-Methylpyrazole D. Wu, B. Potter and A. I. Cederbaum, Depts. of Biochemistry and Medicine, Mt. Sinai School of Medicine, N.Y., NY.

Cytochrome P-450 IIE1 is induced by ethanol, pyrazole, and 4-methylpyrazole (4MP). This P-450 plays a role in the metabolism of agents which are hepatotoxic, especially in alcoholics. The mechanism by which such compounds induce P-450 IIE1 is not clear but may relate to a post-translational level. Hepatocytes were isolated from control rats and rats treated with either pyrazole or 4MP IIE1, plated on collagen and incubated in a serum-free hormonally defined medium containing 1.5% DMSO. P-450 IIE1 was quantitated by Western blots and P-450 IIE1 catalytic activity was determined by assaying for dimethylnitrosamine N-demethylase (DMND) activity. In cultures from non-induced hepatocytes, the content of P-450 IIE1 fell to 76, 6, 5, 31 and 1% of the value of the freshly prepared hepatocytes after 1, 3, 6 and 9 days in culture. DMND activity paralled the content of P-450 IIE1. The 4MP treatment increased the amount of P-450 IIE1 7-fold and elevated DMND activity 4-fold. The decline in P-450 IIE1 and DMND activity was more rapid in cultures from the 4MP-induced rats; P-450 IIE1 fell to values of 77, 31, 3 and 3% and DMND activity fell to values of 62, 30, 7 and 6% after 1, 3, 6, and 9 days in culture. A similar rapid decline was observed in cultures from pyrazole-treated rats. The addition of 4MP *in vitro* the culture medium helped to stabilize both the P-450 IIE1 and DMND activity in cultures from induced and non-induced rats.

Stabilization and Maintenance of Cytochrome P-450 IIE1 in Primary Hepatocyte Culture by 4-Methylpyrazole ***(continued)***

Percent Control Activity

Culture	P-450 IIE1 −4MP	P-450 IIE1 +4MP	DMND Activity −4MP	DMND Activity +4MP
6 days non-induced	31	52	20	57
3 days induced	31	59	30	48
6 days induced	3	21	7	22

These results indicate that 4MP stabilizes P-450 IIE1 and helps maintain catalytic activity of this isozyme in primary cultures. The induced enzyme is especially labile and declines very rapidly in the absence of a stabilizing inducer or ligand.

Hepatocellular ^{22}Na$^+$ Uptake: Effect of Oleate D. Sorrentino, K Van Ness, PD Berk, Liver Unit, Departments of Medicine and Surgery, Mount Sinai School of Medicine, New York, NY.

Studies in isolated hepatocytes, membrane vesicles and perfused liver suggest that hepatic oleate uptake is Na$^+$-coupled and potential sensitive. However, we and others have been unable to show Na$^+$ dependence of oleate uptake in isolated adipocytes and cardiac myocytes, cell types in which the uptake process also conforms to a carrier mediated mechanism. Furthermore, we have shown (Hepatology 7:1036) that in isolated hepatocytes the apparent Na$^+$ and energy dependence of oleate uptake may be a consequence of the experimental conditions employed.

To further examine this issue a rapid filtration technique was used to study ^{22}Na$^+$ uptake by isolated hepatocytes employing Hanks' Hepes (±5 mM NaHCO$_3$), pH 7.4, with or without 1000 μM oleate (complexed with 250 μM albumin). Because of the well-established link between Na$^+$ uptake and alanine, taurocholate, and monensin, the latter compounds (5 mM, 100 μM and 10 μg/ml respectively) were used as positive controls. In the presence of NaHCO$_3$, basal uptake of 150 mM ^{22}Na$^+$ was 11.9 ± 1.7 nmol/min/10^6 cells. Addition of alanine, taurocholate and monensin increased ^{22}Na$^+$ uptake by 45, 25 and 157%. The uptake of ^{3}H-taurocholate and ^{3}H-alanine suggested a 1:1 to 2:1 stoichiometry. Addition of oleate did not change basal uptake (11.2 ± 1.2 nmol/min/10^6 cells); under these conditions, ^{3}H-oleate uptake averaged 5.3 ± 0.8 nmol/min/10^6 cells. In the absence of NaHCO$_3$, basal ^{22}Na$^+$ uptake was 5.5 ± 0.2 nmol/min/10^6 cells while alanine, taurocholate and monensin increased the uptake by 25, 27 and 85%. Again, the presence of oleate did not modify basal ^{22}Na$^+$ uptake (5.7 ± 0.4 nmol/min/10^6 cells) while ^{3}H-oleate uptake averaged 4.4 ± 0.8 nmol/min/10^6 cells.

Conclusions: In isolated hepatocytes ^{22}Na$^+$ uptake is increased by alanine, taurocholate and monensin but not by oleate even though the uptake of the latter is sufficient to elicit a detectable effect. Although it cannot be excluded that a portion of Na$^+$ uptake is linked to oleate and vice versa, these data indicate that such a linkage, if present, involves a very small portion of their total uptake.

Plasma Fatty Acid Concentration and Hepatocellular Fatty Acid Uptake: The Effect of Diabetes and High Fat Diet D Sorrentino, E Broderick, D Stump, K Van Ness, Liver Unit, Dept. of Medicine, Mount Sinai School of Medicine, New York, NY.

Previous studies (Gastro 96:662) have shown that carrier mediated hepatic uptake of free fatty acids (FFA) is increased during starvation, a condition associated with increased plasma FFA concentrations

Plasma Fatty Acid Concentration and Hepatocellular Fatty Acid Uptake: The Effect of Diabetes and High Fat Diet *(continued)*

($[FFA]_p$). In the present study we explored the hypothesis that, in analogy with other systems (e.g. those responsible for the uptake of amino acids and glucose) the process of hepatocellular FFA uptake may be modulated by plasma substrate concentrations.

For this purpose we used a rapid filtration technique to measure initial ^{3}H-oleate uptake velocity (from 0 to 10 sec at 2 sec intervals) by hepatocytes isolated from male diabetic (induced by streptozotocin 65 mg/kg [D]) and fat fed (35% lard in the diet for 6 weeks [F]) SD rats, conditions also known to be associated with increased $[FFA]_p$. Appropriate controls were used for each group. Uptake was studied at oleate:albumin ratios from 0.1:1 to 2:1 keeping albumin constant. $[FFA]_p$ was measured by spectrophotometry. In all groups initial uptake, reflecting influx and not metabolism, was saturable with increasing unbound oleate concentrations. Compared to controls, Vmax values (pmol/min/mg protein) were significantly increased in the experimental groups; for D: 1070 ± 107 vs 850 ± 50, $p < 0.05$; for F: 1230 ± 156 vs 886 ± 80, $p < 0.05$. By contrast, Km values (nM) were unchanged by treatment; for D: 126 ± 28 vs 100 ± 10, $p > 0.5$; for F: 100 ± 17 vs 100 ± 12. As expected, $[FFA]_p$ (mM) was increased in both D (0.47 ± 0.08 vs 0.30 ± 0.03, $p < 0.05$) and F (0.83 ± 0.14 vs 0.27 ± 0.02, $p < 0.02$). Finally, when Vmax values for experimental and control groups were plotted against the respective $[FFA]_p$ the data described a significant ($r = 0.97$) positive linear relationship.

Conclusions: Vmax for oleate uptake by isolated hepatocytes is increased following diabetes and a high fat diet, conditions associated with higher $[FFA]_p$. Furthermore, the data indicate a significant relationship between these two parameters. These observations suggest that, in analogy with other transport systems, the hepatic uptake of FFA may be modulated by the plasma concentration of substrate.

BSP/Bilirubin- and Organic Anion-Binding Proteins, Similar 54 kDA Plasma Membrane Glycoproteins with High Affinities for Organic Anions, Are Transcribed from Different mRNAs P. D. Berk, S. Patel and L. M. Isola, Liver Unit (Department of Medicine), Mt. Sinai School of Medicine, New York, NY.

BSP/bilirubin binding protein (BSP/BR-BP) and organic anion binding protein (OA-BP) are both 54 kDA integral glycoproteins of the liver cell plasma membrane (LPM). By immunofluorescence, BSP/BR-BP is restricted in its distribution to the LPM. By ELISA, which does not distinguish membrane from intracellular antigen, OA-BP is widely distributed, with highest levels in heart. The message for OA-BP, identified by immunoscreening a rat liver cDNA library in bacteriophage λgt11, has been cloned and sequenced, and found to be identical to that for the β subunit of the widely distributed mitochondrial enzyme F_1-ATP synthase (Hepatol 8:1254, 1988).

Using a rabbit antibody against BSP/BR-BP, we isolated and cloned into pGEM-1 plasmid vectors 3 cDNA fragments (A: 550 bp; B: 600 bp; and C: 1350 bp) from the same library. Corresponding fusion proteins produced in *E. coli* reacted with antibodies against both BSP/BR-BP and OA-BP, indicating that the proteins shared immunologic epitopes (Hepatol. 8:1264, 1988).

We now report that fragment C encodes in *E. coli* for a fusion protein which binds BSP. Using the [^{32}P]-labeled pGEM containing the cloned fragment 3 insert as a probe, hybridization in slot blot analyses was observed only with mRNA from rat liver; other tissues, e.g. heart, were negative. By Northern analysis, the message encodng for BSP/BR-BP in rat liver is 2.3 kb. Restriction mapping reveals that fragment C is different from OA-BP mRNA; e.g. Bam HI, Bgl I and Xba I sites present in OA-BP are lacking in BSP/BR-BP, while Hind III, Hinc II and Xho I sites found in BSP/BR-BP (fragment C) are lacking in OA-BP. Partial sequence analysis at both the 5′ and 3′ ends of fragment C does not show a high degree of homology with OA-BP.

By contrast, the first 231 bases of fragment C show 87% homology with the sequences reported for exons 1–3 of rat liver arginase; thereafter, the sequences diverge. Fragment C corresponds to a portion of a liver specific 2.3 kb message which, in *E. coli*, encodes for a BSP binding protein. The message is different from that which encodes for OA-BP.

Neoplastic Diseases and Medical Oncology

Augmentation in vitro of Interleukin-2 Activated Killer (LAK) Cell Mediated Tumor Cell Lysis by Monoclonal Antibody B. T. Motwani, P. A. Paciucci, J. Ryder, H. Arkin, J. F. Holland, Box 1129, Dept. of Neoplastic Diseases, Mt. Sinai School of Medicine, New York, NY.

We have investigated adoptive immunotherapy with interleukin-2 in advanced human cancers either alone, or with lymphokine activated killer (LAK) cells or in combination with chemotherapy with encouraging results.[1] We sought to determine if addition of appropriate monoclonal antibody would enhance antitumor responses in vitro.

We investigated the ability of IL-2 activated lymphocytes to lyse colon carcinoma cells in the presence of 17-1A[2], an IgG2a monoclonal antibody (MoAb) against a membrane associated glycoprotein found on human colon carcinoma cells. Although the three human carcinoma cell lines used all reacted (by indirect immunofluorescence) with 17-1A, they were differently susceptible to lysis mediated by: a) fresh unstimulated peripheral blood lymphocytes (PBL); b) PBL in the presence of 17-1A; c) normal lymphocytes activated in vitro with IL-2, 500 units/ml (LAK^{vitro}); and d) lymphocytes activated in vivo, obtained from patients receiving IL-2 immunotherapy (LAK^{vivo}).

Regardless of their varied susceptibility to these cytolytic mechanisms, all three lines were maximally lysed in the presence of 17-1A when the effector cells had been activated in vitro or in vivo with IL-2.

These data suggest that, whereas these three colon carcinoma lines possess varying degrees of susceptibility to anti-tumor cell mediated cytolytic responses (thus mimicking the heterogeneity experienced in the clinic), two of the three were additionally lysed when two different antitumor immunomodulatory treatments were combined.

Additional preliminary data were obtained from the testing of NCI-LYM-1[3], a monoclonal antibody directed at an HLA-Dr surface antigen on normal and malignant B lymphocytes. Two human B lymphoma/leukemia lines, developed in our laboratories[4] were lysed in vitro by interleukin-2 activated killer cells from normal volunteers and enhanced tumor cell lysis was seen on addition of the monoclonal antibody.

The results suggest that the combination of IL-2 with ADCC-inducing MoAbs can result in synergistic cell-mediated antitumor effects. Clinical trial appears imperative.

Combination Cytoreductive Differentiation Therapy with 5-FU and HMBA Samuel Waxman, M.D., Barbara M. Scher, Ph.D., Nella Hellinger, M.S., William Scher, M.D., Division of Medical Oncology, Box 1178, Mount Sinai School of Medicine.

We investigated the effects of 5-fluorouracil (5-FU), an inhibitor of thymidyate synthetase and hexamethylene bisacetamide (HMBA), on the growth and differentiation of murine erythroleukemia (MEL) cells. MEL cells were first treated with 5-FU, washed and then treated with various concentrations of HMBA, dimethylsulfoxide (DMSO) or N-methylformamide (NMF). These three inducers of differentiation markedly inhibited MEL cell growth and increased MEL cell death in a dose- and time-dependent manner if given after MEL cells were exposed to 5-FU. Eighty percent of the MEL cells were non-viable after treatment with 5-FU and Leucovorin followed by HMBA. 5-FU or 5-FU with Leucovorin significantly inhibited MEL cell growth and slightly increased MEL cell death while HMBA had little effect on MEL cell growth or viability. When placed in fresh medium for 6 days following drug treatments MEL cells rapidly recovered from the 5-FU growth inhibition. There was inhibition of cell growth without loss of viability in MEL cells previously treated with HMBA. In contrast, a profound and prolonged growth inhibition with 98% cell death occurred in MEL cells previously treated with 5-FU and HMBA.

The marked increase in cell death following 5-FU and HMBA treatment may be a consequence of the inhibition of DNA repair perhaps due to a decrease in DNA ligase activity and/or an increase in DNA nuclease activity following HMBA-induced commitment to ter-

Combination Cytoreductive Differentiation Therapy with 5-FU and HMBA *(continued)*

minal cell division. Pre-treatment with 5-FU, shown here to be a weak inducer of MEL cell differentiation, enhances the subsequent HMBA induction of differentiation and terminal cell division in some of the MEL cell population. These data support the concept that 5-FU treatment, which results in imbalance of intracellular deoxyribonucleoside triphosphate pools, is responsible for reversible cell growth inhibition. However, the DNA breaks which occur as a result produce the lethal event to the cell. The marked increase in cell death following 5-FU and HMBA treatment may be a consequence of the inhibition of DNA repair due a decrease in DNA ligase activity and/or an increase in DNA nuclease activity following HMBA-induced commitment to terminal cell division.

This example of cytoreductive differentiation therapy may be the basis of a new approach to cancer chemotherapy and may aid in reducing the toxicity of certain chemotherapeutic agents, while maintaining or even increasing their therapeutic effects.

Effect of IL-2 in vitro and in vivo on platelet function L. Oleksowicz, P. A. Paciucci, J. Rand, J. Ryder, J. Holland, Department of Neoplastic Diseases and Division of Hematology, Mt. Sinai Medical Center, N.Y., NY.

Twenty-six of 66 cancer patients treated with recombinant IL-2 by constant infusion developed significant (grade 2–4) thrombocytopenia associated with increased marrow megakaryopoiesis. We evaluated the effects of IL-2 on platelet function. Seven of eight patients developed platelet clumping on peripheral smears during the first week of treatment which was reversed on discontinuation of the infusion. Whereas platelet-rich plasma (PRP) incubated with varying concentrations of IL-2 showed normal aggregation to epinephrine and ADP, both the rate of aggregation and maximum aggregation were reduced when whole blood was incubated for 5–10 minutes with IL-2, 100–2000 U/ml. This effect was not seen in PRP lacking additional cellular components.

Ratio	Dose of IL-2, U/ml		
IL-2/Control	100 U/ml	500 U/ml	2000 U/ml
MS*	0.6 (.09)**	0.4 (.116)	0.4 (.12)
MMA***	0.4 (.15)	0.4 (.116)	0.4 (.12)
P-value (MS;MMA)	.0009;.019	.002;.004	.004;.006

* Mean Slope, ***Mean Maximum Aggregation, **Standard Error

Levels of thromboxane B2 (TXB2) and prostaglandin E2 (PGE2), potent mediators of platelet aggregation, were assayed by radioimmunoassay in the supernatants of IL-2 stimulated lymphocytes and monocytes. IL-2 induced a dose-dependent production of PGE2 and TXB2 and a 1.4- to 3.3-fold increase of both factors within 10 minutes of addition.

IL-2 therefore indirectly induces qualitative defects of platelet function. This effect may be the result of its stimulation of eicosanoid synthesis or release in lymphocytes and monocytes.

Quantification by GC/MS of Separated Enantiomers of Arabinitol as a Same-Day Blood Test for the Differential Diagnosis of Disseminated Candidiasis John Roboz, Ph.D., Edward Nieves, B.S., and J.F. Holland, M.D., Department of Neoplastic Diseases, Box 1247, Mount Sinai School of Medicine.

The use of serum total (D + L optical isomers) arabinitol concentrations to diagnose and monitor disseminated visceral candidiasis in immunosuppressed patients has been limited because of the inability to differentiate between increased arabinitol of fungal and non-fungal (i.e., due to renal dysfunction) origin (1). There is evidence that fungal arabinitol is all D (2) and endogenous arabinitol is a mixture of D and L isomers (3). Our objective was to develop a GC-MS technique using a chiral column for the direct chromatographic separation and quantification of the D and L optical isomers of arabinitol in serum and urine.

To differentiate increased arabinitol due to fungal and nonfungal origin, O-trifluoroacetyl derivatives of the enantiomers were separated using α-perpentylated cyclodextrin glass capillary columns (4) and

Quantification by GC/MS of Separated Enantiomers of Arabinitol as a Same-Day Blood Test for the Differential Diagnosis of Disseminated Candidiasis *(continued)*

measured by selected ion monitoring of the M-OCOCF$_3$ ions (internal standard: fully deuterated arabinitol). Mean ± s.d. D/L in normal serum (n = 21) was 1.40 ± 0.42 (range: 0.72–2.21). The D/L ratios of normals and candidiasis-free cancer patients (n = 10) were not significantly different (two-tailed t-test). D/L ratios greater than the normal mean + 2 s.d. (>2.2), were considered outside normal range. D/L was >2.2 in 10 of 12 confirmed candidiasis cases with one false negative and one borderline. Renal dysfunction without candidiasis yielded normal D/L despite high arabinitol concentrations. D/L in normal urine was nearly identical to that in serum despite 60 times larger concentrations.

D/L ratios, determined by peak heights or areas, can be used without the need to determine concentrations for the same day, accurate diagnosis of early visceral candidiasis.

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Nephrology

Renal Epidermal Growth Factor (EGF) Production Decreases and EGF Receptors Increase Following Renal Ischemia R. Safirstein, P Price, and R. C. Harris, Mt. Sinai School of Medicine, NY, NY and Vanderbilt University, Nashville, TN.

Urine is a rich source of EGF, and the kidney contains high concentrations of mRNA for the EGF percursor, preproEGF. We have recently reported reduced levels of preproEGF mRNA and urinary EGF excretion after renal artery clamping (Clin. Res. 36:597A) and now report the time course of changes of renal EGF production and changes of renal EGF receptor concentration following 50 minutes of vascular clamping.

Measurement of urinary EGF excretion by radioreceptor assay revealed a 90% decrease in EGF excretion within 1 hour post insult, and a return to only 5% of control by day 4. Poly (A$^+$) mRNAs were isolated by guanidinium isothiocyanate extraction and oligo-dT chromatography. Northern blot hybridization revealed a 60% decrease in preproEGF mRNA by 2 hours and virtual absence by 12 hours post insult, with only a 1% return towards normal by 4 days. In contrast, significant increases in ^{125}I-EGF binding were noted in membrane preparations prepared from both cortex and inner medulla, compared to the contralateral kidney. In inner medulla, EGF binding was increased 220% within 24 hours ($n = 4$; $p < 0.05$). At 4 days high affinity binding increased from 9.3 to 21.9 fmol/mg protein (n = 2). In cortex, binding increased from 1.2 ± 0.3 to 2.6 ± 0.3 fmol/mg protein ($n = 6$; $p < 0.005$). There were no differences in the basolateral marker, Na-K ATPase or the apical marker, alkaline phosphatase, between membrane preparations. There was no change in EGF binding affinity in cortex or inner medulla.

In summary, these studies demonstrate that ischemic renal insult reduces renal preproEGF mRNA levels and urinary EGF excretion, while at the same time the kidney expresses an increased number of EGF receptors. These data are consistent with regulation of renal EGF receptor density by intrarenal EGF production and suggest a possible functional role for urinary EGF. Increased EGF receptor number may also be a response to renal injury.

Ontogeny of Na/H Antiporter Activity in Rabbit Renal Brush Border Membrane Vesicles (BBMV) Jeanne C. Beck, Michael S. Lipkowitz, and Ruth G. Abramson, Division of Nephrology, Box 1243, Mount Sinai Medical Center.

The development of the Na/H antiporter was studied in renal BBMV prepared by Mg precipitation from near term fetal (29–31 days) and adult rabbits using isotopic and fluorescent techniques. The kinetics of the antiporter studied by $^{22}Na^+$ uptake revealed that the K_ms for Na^+ were not significantly different; however, in the fetal vesicles the V_{max} was only 25% of that in the adult.

These data were confirmed by a fluorescent assay using the pH sensitive probe, acridine orange: the K_ms were not different, but the V_{max} was again significantly lower in the fetal BBMV. Conductive Na^+ movement was estimated from amiloride-insensitive $^{22}Na^+$ uptake and the rate of alkalinization induced by K^+, an ion whose relative conductance was found to be similar to that of Na^+. Although relative Na^+ conductance was significantly greater in fetal BBMV, the lower V_{max} in fetal BBMV could not be ascribed to this factor. Maternal administration of betamethasone (50 μg/kg intramuscularly) for 2 days prior to delivery significantly increased the V_{max} of the antiporter to levels observed in the adult; K_m was unaffected. Na/K ATPase activity increased 4 fold after betamethasone, but the specific activities of 4 BB marker enzymes in the homogenate were unchanged.

These data indicate that there is a developmental increase in BB Na/H exchange which is the result of an increase in the number and/or the turnover number of the carriers. Further, these data suggest that the postnatal increase in antiporter activity may be related, in part, to the surge in glucocorticoid concentration that occurs perinatally.

Nuclear Medicine

Gastrointestinal Bleeding Scintigraphy: A Retrospective Review C. J. Palestro, D. Spagnoli, C. K. Kim, S. J. Goldsmith, Box 1141, Mount Sinai Medical Center, New York, NY.

This retrospective study evaluated the accuracy of Tc99m tagged red cell (RBC) scintigraphy for evaluation of gastrointestinal bleeding at Mount Sinai Medical Center. 64 patients (pts) were included in the study. Cells were labeled in vitro. Imaging continued until a bleeding focus was identified & localized or, when negative, through 24 hours. A pt. was considered actively bleeding if a lesion was subsequently documented by non-nuclear techniques (37 pts) or if a pt's hematocrit decreased by at least 3 percentage points during the study or failed to increase following transfusion (4 pts). Results were: 41 studies true positive; 19 true negative, 0 false positive, 4 false negative (91% sensitivity, 100% specificity, 94% accuracy).

CORRECTLY LOCALIZED BLEEDING SITES

LOCATION	(Time vs Location) 1 HR	4 HR	12 HR	24 HR	TOTAL
Left Colon	5	6	0	1	12
Right Colon	2	2	1	2	7
Cecum	2	0	1	1	4
Gastroduodenal	1	1	0	2	4
Rectosigmoid	1	0	1	0	2
Jejunal	1	1	0	0	2
Transverse Colon	1	0	0	0	1
Diffuse Colonic	0	1	0	0	1
Total	13	11	3	6	33
%	39.4%	33.3%	9.1%	18.2%	100%

RBC correctly localized 33 pts. with docmented lesions (accuracy for localization 89%). 2 incorrect localizations occurred during the first hour of imaging (jejunal bleed described as left colon & left colon bleed described as jejunal) and 2 occurred at 24 hours (cecal activity in a pt. with gastric bleed, & transverse colon activity in a pt. with a cecal bleed.

Gastrointestinal Bleeding Scintigraphy: A Retrospective Review *(continued)*

This study reconfirms the exquisite sensitivity & specificity of RBC scintigraphy to evaluate GI bleeding. Our data reemphasizes the importance of continued imaging of negative studies beyond 4 hours. 24 hour images alone may be misleading however and must be interpreted cautiously.

Delayed Biliary to Bowel Transit on Cholescintigraphy after Cholecystokinin Pretreatment and Its Postulated Mechanism C. K. Kim, C. J. Palestro, D. Spagnoli, R. W. Solomon, P. Stritzke, S. J. Goldsmith, Box 1141, Mount Sinai Medical Center, New York, NY.

This study assesses the influence of cholecystokinin (CCK) pretreatment (PRx) on biliary to bowel transit (BBT) of Tc-99m disofenin (IDA).

Part I: After overnight fast, 14 volunteers (V) underwent 2 separate cholescintigraphies (CS) 2 days apart. 30 min before 1CS, each V received 30 ng/kg CCK. Following injection of 5 mCi IDA, serial images were obtained for 2 hrs.

BBT in CS without CCK was <60 min in all 14V (<30 min in 12/14). BBT in CS with CCK was <30 min in 7/14V. No bowel activity was present at 2 hrs in the remaining 7 ($P = 0.006$ by chi-square test).

Gallbladder filling (GBF) was seen at 10.2 ± 4.2 min without CCK and 8.8 ± 4.0 min with CCK ($P = 0.15$).

Part II: Retrospective analysis of 50 consecutive CS after CCK PRx on patients (pts) with suspected acute cholecystitis revealed: (a) In all 19 pts with no GBF and 2 pts with GBF $\geq$ 1 hour (total 21 pts), BBT was <30 min. (b) In 27 pts with GBF < 30 min, BBT < 30 min in 6, 30 $\leq$ BBT < 60 in 8, and BBT $\geq$ 60 in 13. (c) In 2 patients with 30 $\leq$ GBF < 60, BBT < 30 in 1 and BBT $\geq$ 60 in 1 ($P \leq 0.001$ by chi-square test).

In summary (1) CCK PRx produces significantly delayed BBT in a large % (50% in our study) of people; this should not be interpreted as abnormal. (2) Postulated mechanism was preferential GBF due to GB relaxation and/or sphincter constriction after the effects of CCK (GB contraction & sphincter relaxation) disappeared. The finding of normal BBT in all pts without GBF suggests that the latter mechanism is unlikely.

Pulmonary Medicine

Does Soybean Shell Extract Enhance the Constrictor Effect of Carbachol on Airway Smooth Muscle? Edwin Neil Schachter, M.D., Eugenia Zuskin, M.D., Theodore J. Witek Jr., Dr.P.H., Sora Lee, Zvi Marom, M.D., Satindra K. Goswami, Ph.D., Saul Maayani, Ph.D., Department of Medicine, Community Medicine and Pharmacology, Box 1232, Mt. Sinai Medical Center, NY.

Previous reports of soy mill workers suggest that these workers are susceptible to an occupational asthma (Amer J Industrial Med 14:157–65, 1988). Such airway diseases are frequently accompanied by hyperreactivity to methacholine. In a previously described in vitro model using guinea pig trachea GPT (Amer Rev Resp Dis 137:297, 1988) we sought to characterize the effect of soy bean shell extract (SBSE) on the standard carbachol dose response.

Additionally we studied the effect of airway epithelium on this response. Extracts were prepared using 1 gram of soy bean shell in 10 ml of sterile water. We measured the isometric tension developed in GPT suspended in an organ bath containing 20 ml of Krebs Buffer at 37C. Each GPT was divided into 4 segments so that each animal served as its own control for the studies. SBSE was added to the bath in aliquots of 10, 30, 100, 300, 1000 ul. The protocol consisted of performing a dose response study with carbachol (10^{-8} to 3×10^{-5} M) before and after adding SBSE. Krebs was added to tissues from the same animal as a control performed concurrently. $N = 11$ guinea pigs were studied in this protocol. Additionally $n = 7$ guinea pigs were studied in which half of the GPT segments had the epithelial lining removed (Ep−) with the balance of the GPT serving as a control (Ep+). SBSE elicited a dose dependent contraction of GPT with a maximal response (Emax) of 69 ± 13.8% of the maximal pre-SBSE carba-

Does Soybean Shell Extract Enhance the Constrictor Effect of Carbachol on Airway Smooth Muscle? *(continued)*

chol response. Concentration response curves performed after SBSE showed an enhancement of carbachol response Emax = Emax (pre) − Emax (post)/Emax (pre) = 36%, however, this was no different than that seen in the control experiment Emax = 30% (t = .3, NS). Similar findings were noted with Ep−. The response to carbachol in Ep− following SBSE was no different than the response to carbachol in Ep+ following SBSE.

We conclude that SBSE causes a dose related constriction of GPT in vitro; this is unaccompanied by a specific sensitization of the airways to carbachol. Finally removal of airway epithelium does not enhance carbachol responsiveness following SBSE.

Vessel Wall Thrombogenicity Following Excimer vs Thermal Laser Angioplasty Jonathan D. Marmur, Timothy A. Sanborn, Juan J. Badimon, Renate Dische, Lina Badimon, Dimitrios Alexopoulos, Valentin Fuster, Mount Sinai Medical Center, New York, NY.

Vessel wall thrombogenicity (VWT) following laser angioplasty (LA) is an important but unresolved issue. Therefore, atherosclerotic rabbit iliac arteries were randomized to treatment with 308nm XeCL excimer (EXC) LA (30 m Joules/mm^2, 25Hz) or argon thermal (THERM) LA (10 watts × 5 sec). Two hrs post LA results were assessed in terms of change in % angiographic luminal stenosis (△ %STEN), complications (COMP) (spasm, perforation), Indium^{111}-labeled platelet (PLAT) deposition, histological damage defined as minimal (MIN DAM) vs. severe (SEV DAM), ie. (vs.) 50% coagulation necrosis of intima, mild vs. severe inflammation.

	Δ% STEN*	COMP	PLAT × 10^6/cm*	SEV DAM
EXC (n = 7)	23 ± 12	n = 0	21 ± 27	n = 1
THERM (n = 7)	27 ± 6	n = 3	49 ± 48	n = 4

(* x ± SD) (p = NS for all groups)

When VWT was assessed as a function of histology, vessels with SEV DAM (n = 5) had greater PLAT deposition than those with MIN DAM (n = 12) (73 ± 46 × 10^6 PLAT/cm, $p < .01$).

These data suggest that VWT following LA is more a function of the degree of vessel wall damage (VWD) than the exact nature of the laser energy being utilized. EXC LA appears to be associated with lesser degrees of VWD and fewer COMP than THERM LA.

Effects of Isoproterenol and VIP on Adenylate Cyclase Activity in a Mucus-Secreting Adenocarcinoma Cell Line Jonathan Tzvi Klein, M.D., Satindra Goswami, Ph.D., Saul Maayani, Ph.D., Zvi Marom, M.D., Division of Pulmonary Medicine, and Department of Anesthesiology, Box 1232, Mount Sinai Medical Center.

The physiological functions of a wide range of tissue and cell types are known to be modulated by locally released agents. These agents act simultaneously at distinct receptors on the same cell membrane, causing synergistic or functionally antagonistic responses. The secretion of mucous glycoproteins (MGP's) by an adenocarcinoma cell line in culture (Ishikawa cells) has been shown to be modulated by β-adrenergic and Vasoactive Intestinal Peptide (VIP)-ergic receptors (Amin et al, 1989).

Parallel studies were undertaken to better understand the interactions of these agents in Ishikawa cells. Lysed Ishikawa cells were incubated for 5 minutes in the presence of varying concentrations of Isoproterenol (ISO) and/or VIP. Conversion of α-[^{32}P]-ATP or [^{32}P]-cAMP was measured (using a variation of the method described by Salomon), yielding an index of adenylate cyclase activity expressed as percent above baseline. ISO induced a concentration-dependent, saturable response with an E_{max} of ≈600% above baseline and an EC_{50} of ≈4 × 10^{-7} M. VIP stimulated a more robust response with an E_{max} of more than 2000% above baseline and an apparent EC_{50} of ≈4 × 10^{-8} M. The effects of VIP and ISO were less than additive.

These studies, along with the physiological experiments noted above, indicate that Ishikawa cells are a suitable model for studying the physiology of MGP secretion. Our data suggest that, in Ishikawa cells, VIP and β-adrenergic receptor agonists modulate MGP release by their actions on distinct adenylate cyclase linked membrane receptors. (Supported by NIH grant HL37254).

Effects of Isoproterenol and VIP on Adenylate Cyclase Activity in a Mucus-Secreting Adenocarcinoma Cell Line *(continued)*

Functional Antagonism between Neurotransmitters in the Control of Mucous Glycoprotein Secretion in a Model of Epithelial Cells D. N. Amin, S. Goswami, S. Maayani, Z. Marom, Divisions of Anesthesia and Pulmonary Medicine, Box 1232, Mount Sinai Medical Center.

The effects of vasoactive intestinal polypeptide (VIP) and isoproterenol on the in vitro release of radioactively labeled mucous glycoprotein (MGP) by Ishikawa adenocarcinoma cell cultures were investigated. These effects were compared to the effect of each neurotransmitter alone, combined and in the presence of carbachol a potent cholinergic stimulator of MGP release.

Using four cell culture plates for each concentration, a dose dependent inhibition of baseline MGP release by VIP was established. Concentrations of 10^{-6} to 10^{-13} molar VIP produced a 52 ± 5%–4 ± 5% inhibition of base line MGP secretion respectively. Isoproterenol produced a similar dose dependent reduction of MGP from baseline, 10^{-5}–10^{-11} molar Isoproterenol produced a 45 ± 5%–4 ± 5% inhibition respectively. Carbachol alone at 10^{-7} molar produced an 80 ± 10% increase of MGP release from baseline secretion. The carbachol enhanced secretion was inhibition by VIP and Isoproterenol by a much greater degree to a level significantly below baseline secretion. VIP had a greater inhibitory effect than isoproterenol on MGP release at the same molar concentrations. When maximal inhibitory concentrations of VIP (10^{-6} molar) and isoproterenol (10^{-5} molar) were added together to carbachol stimulated cells the inhibition was greater than for each alone but not additive.

These effects on Ishikawa cell line MGP release suggest functional antagonism between cholinergic induced MGP release and the inhibitory effect on MGP release by VIP receptor and β receptor mediated events. In view of the existence of VIP immunoreactive nerves in human respiratory submucosa and the presence of specific receptors to VIP in close proximity to respiratory submucosal glands it is postulated that a similar state of functional antagonism may exist between cholinergic and VIPergic systems in human airways. A reduction or absence of VIP may upset this balance and result in mucus hypersecretion.

The Shape of the Maximal Expiratory Flow-Volume Curve in Induced Airway Constriction and Relaxation in Healthy and Asthmatic Subjects John H. Russomanno, M.D., Theodore J. Witek Jr., Dr.P.H., Edwin Neil Schachter, M.D., Departments of Medicine and Community Medicine, Box 1232, Mt. Sinai School of Medicine.

We have previously described a new lung function parameter, angle β, which characterizes the maximal expiratory flow volume (MEFV) curve's shape, and have validated its usefulness in epidemiologic data analysis (Chest 94:799–806, 1988). Since acute changes in the shape of the MEFV curve are often visually apparent in induced airway constriction and relaxation, we examined the change in angle β in a series of bronchial provocation studies.

Angle β was measured in 15 asthmatic and 22 healthy subjects (HS) following induced bronchoconstriction with methacholine at the highest methacholine concentration tested: 28.7 ± 5.6 mg/ml for asthmatics and 98 ± 2.3 mg/ml for HS (mean ± SE). Angle β was also studied in 20 asthmatics and in 22 HS following relaxation with an inhaled bronchodilator. Angle β was significantly decreased following induced airway constriction and significantly increased following airway relaxation in both groups:

	Group	Pre-*	Post-	P
Constriction:	Asthma	175.9 ± 3.0†	165.1 ± 2.2	<0.001
	HS	188.1 ± 3.3	180.9 ± 3.2	=0.017
Relaxation:	Asthma	168.0 ± 2.8	174.7 ± 3.4	=0.005
	HS	187.4 ± 3.1	190.9 ± 3.0	<0.001

* mean ± SE †measured in degrees

The Shape of the Maximal Expiratory Flow-Volume Curve in Induced Airway Constriction and Relaxation in Healthy and Asthmatic Subjects *(continued)*

The magnitude of change in angle β was greater for asthmatics than for HS. These changes were not significantly correlated with the baseline lung function measures as the percent of predicted FEV1 in each group. The day-to-day correlation of angle β was statistically highly significant ($r = 0.92$; $P < 10^{-6}$). In the asthmatics, angle β measured at the PC20 was significantly less than angle β measured at baseline (175.9 *vs* 165.2; $P < .0001$).

We conclude that angle β is a potentially useful parameter for quantitating induced bronchoconstriction and bronchial relaxation in both asthmatic and HS.

The Spectrum of Pulmonary Disease due to Mycobacterium avium-intracellulare A. S. Teirstein, B. Damsker, P. K. Kirschner, A. R. Gribetz, M. T. Chuang, and M. J. Rosen, Mount Sinai Medical Center, New York, NY.

Despite reports of patients with pulmonary disease due to MAI from New York and Canada, most physicians fail to recognize MAI as a major pathogen in all locations. During the past 15 years, we have identified 194 patients at The Mount Sinai Hospital, N.Y. with pulmonary disease primarily or secondarily complicated by MAI. These infections have presented with four distinct clinical patterns:

1. Pulmonary nodules ("tuberculomas") indistinguishable from pulmonary neoplasm—41
2. Chronic bronchitis and/or bronchiectasis with sputum repeatedly positive for MAI and/or granulomas on biopsy—48
3. Cavitary lung disease and scattered pulmonary nodules mimicking *M. tuberculosis* infections—21
4. Diffuse pulmonary infiltrations in immunocompromised hosts, primarily AIDS—84

Pulmonary disease due to MAI infection has become an important common clinical problem in general hospital populations. A variety of treatment regimens are available. Treatment depends upon the clinical setting.

Forced Mid-Expiratory Time: Smoking-Specific Predictive Equations L. K. Brown, M.D., FCCP, A. Miller, M.D., FCCP, M. Pilipski, Division of Pulmonary and Critical Care Medicine, Pulmonary Physiology Laboratory, Mount Sinai Medical Center, Box 1232, New York, NY.

Forced mid-expiratory time (MET), the time required to exhale from 25% to 75% of FVC, has been advocated as a relatively volume-independent measure of obstruction. (ARRD 104:61). Previous estimates of MET have been 0.5–0.64 (Am Rev Tub 72:783), or 0.77 (AARD 107:231). MET has not been systematically studied for effect of age, height, sex, and smoking history.

We analyzed flow-volume loops from 367 normal lifetime nonsmokers and smokers, a random sample of the population of Michigan previously described in detail (ARRD 127:270). MET was calculated from the curve with the largest sum of FVC and FEV^1, collected using ATS guidelines. Linear models including age and/or height (Ht) were considered, with and without log transformation of MET. Male (M) and female (F) non-smokers (NS) and smokers (SM) were analyzed separately. The best models used age and height (in cm) and no transformation:

Group	Intercept	Age Coeff.	Ht Coeff.	R2	P
M,NS	0.403	0.003	0.00079	0.058	0.06
M,SM	−1.193	0.009	0.0091	0.239	0.0001
F,NS	−0.990	0.004	0.0091	0.111	0.0007
F,SM	−0.071	0.001	0.0039	0.015	0.63

Age and height contributed much less to the variability of MET than to spirometric flows previously investigated in this group (Bull Eur Phys Resp 22:589). The largest R^2 was found in the M SM, in which the largest contribution was from age, suggesting a smoking effect. Age and smoking duration alone gave similar R^2 values; the latter was 0.133 with $P = .0007$. Smoking duration did not show a significant effect in F SM, agreeing with our previous study in which duration of smoking affected flows for normal M SM but not F SM.

As age was the major contributor to the value of MET, and that contribution was small, we suggest the use of simplified age-stratified mean values derived from our data (mean ± SD):

Group	Age < 40	Age > 40	P (age <40 vs. >40)
M,NS	0.656 ± 0.175	0.678 ± 0.183	0.58 (NS)
M,SM	0.660 ± 0.173	0.835 ± 0.209	0.0008
F,NS	0.583 ± 0.164	0.691 ± 0.261	0.0089
F,SM	0.603 ± 0.181	0.617 ± 0.230	0.78 (NS)

Forced Mid-Expiratory Time: Smoking-Specific Predictive Equations *(continued)*

Rheumatology

HIV-Associated Polyarteritis Nodosa (PAN) Diagnosed by Rectal Biopsy: Case Report Joanne Valeriano, M.D., Lalita Ravichandran, M.D., and Leslie Kerr, M.D., Division of Rheumatology, Box 1244, Mount Sinai School of Medicine and North General Hospital, NY.

The spectrum of HIV-associated rheumatic syndromes reported in the current literature include Reiter's syndrome, Sjogren's syndrome, myositis, psoriatic arthritis, acute articular syndromes and only three cases of vasculitis. We describe an additional case of PAN in a patient with HIV disease.

A 36-year-old black man with a history of IVDA and HIV seropositivity presented with approximately six months of severe bilateral lower extremity ulcers, fever and the acute onset of diffuse abdominal pain, right foot drop, and gangrene of multiple toes. In-patient evaluation did not reveal evidence of opportunistic infection and was remarkable for severe anemia, guiaic positive stool, an ESR of 132 and negative HBS Ag. Because a diagnosis of amyloidosis was initially entertained, a rectal biopsy was performed which demonstrated acute medium-sized vessel vasculitis with fibrinoid deposition. No infectious organisms or amyloid deposits were noted. He was treated with high dose steroids with rapid healing of the vasculitic ulcers, improvement of the foot drop, resolution of the abdominal pain and anemia and normalization of the ESR.

This case illustrates two important points: PAN may be another manifestation of HIV disease, and rectal biopsy may be an additional minimally invasive means of establishing the diagnosis of PAN.

Factor B Activation in Systemic Vasculitis Joanne Valeriano, M.D., Leslie Kerr, M.D., and Harry Spiera, M.D., Division of Rheumatology, Box 1244, Mount Sinai School of Medicine.

Vasculitis is a clinicopathologic process associated with inflammation and/or necrosis of blood vessels. To date, numerous lab parameters have been investigated; however, none have been shown to be specific for vasculitis. We previously described the presence of Factor-B activation (FBA) product Ba, in SLE patients using a new assay consisting of isoelectric focusing followed by immunofixation. A significant correlation was found between FBA and the presence of cutaneous vasculitis. We then sought to determine whether FBA was present in other vasculitic syndromes.

Plasma from 35 patients with the following vasculitic syndromes were assayed: 6 PAN, 12 GCA, 7 SLE, and 2 RA with cutaneous vasculitis, 2 leukocytoclastic vasculitis, 3 Wegener's, 1 Takayasu's, 1 Behcet's and 2 patients with mononeuritis multiplex. 9 of 16 patients (approx 50%) with active systemic vasculitis had product Ba detected as compared with 0 of 8 patients with inactive systemic vasculitis and 1 of 11 patients with active cutaneous vasculitis.

These observations suggest that alternate pathway activation occurs in patients with active systemic vasculitis and that it may be a marker for generalized ongoing vascular inflammation.

Myositis and Myofibrosis as a Musculoskeletal Complication of Sickle-Cell Disease (SSD) Joanne Valeriano, M.D., and Leslie Kerr, M.D., Division of Rheumatology, Box 1244, Mount Sinai School of Medicine.

To date the literature on musculoskeletal complications of SSD is sparse, containing only reports of osteomyelitis, bony infarction, arthropathy, and a single report of 2 patients with myositis. Acute myositis secondary to muscle infarction in the setting of painful crisis, and subsequent extensive fibrosis, is not appreciated as a complication of SSD.

Herein we describe 4 patients with SSD, all of whom had recurrent episodes of acute myositis as a dominant feature of their painful crises. Clinical manifestations consisted of symmetric, markedly swollen, tender proximal muscle groups. Biopsy in one patient with this syndrome revealed inflammation and focal areas of muscle necrosis. Follow-up of 2 patients documented the evolution of this acute lesion to a chronic state characterized by fibrosis, induration, atrophy and contractures. Muscle biopsy of one patient at this stage revealed increased collagen.

These preliminary observations suggest that this syndrome is quite prevalent in patients with SSD. Further prospective studies should be initiated to define the true prevalence of this entity, and to develop therapeutic strategies to prevent the chronic debilitating and irreversible sequelae.

Treatment of Wegener's Granulomatosis (WG) with Trimethoprim-Sulfamethoxazole (TMP-SMZ) Harry Spiera, M.D., Division of Rheumatology, Box 1244, Mount Sinai School of Medicine.

TMP-SMX may be an alternative to adjunctive treatment for WG, as suggested by the following experience with 6 patients who had biopsy-proven disease. 2 patients were treated with TMP-SMZ alone and are in full remission at > one year of follow-up. Both had sinusitis and pulmonary involvement, 1 had microscopic hematuria, the other myocarditis. 2 patients had progression of disease necessitating cytotoxic therapy while on TMP-SMZ. Both had sinusitis and pulmonary involvement and both developed worsening renal function despite TMP-SMZ therapy. 1 patient had a relapse of sinusitis on TMP-SMZ requiring the use of steroids. 1 patient with sinusitis and pulmonary infiltrates, who relapsed while on cytotoxic therapy, achieved another remission coincident with the use of TMP-SMZ.

This experience suggests that TMP-SMZ is an effective treatment for some WG patients and may be the only agent required. Some patients, however, may not respond and will still require cytotoxic therapy to control the disease.

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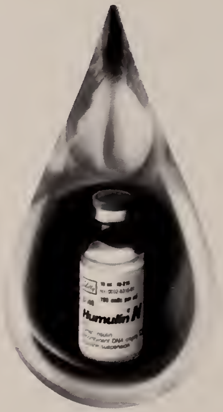

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Grand Rounds

Primary Pulmonary Hypertension:

Modes of Diagnosis and Aggressive Treatment with Vasodilators

Stuart Rich, M.D.

WHAT I hope to review today is the diagnosis and management of a patient with unexplained pulmonary hypertension, and then focus on primary pulmonary hypertension, which has been one of the least understood forms of pulmonary hypertension.

The causes of chronic pulmonary hypertension are many. In this country, the most common cause is lung disease, that is, chronic obstructive airway disease or interstitial lung disease. Any process that elevates left ventricular filling pressure can also function backward to create pulmonary hypertension. Congenital heart disease associated with a left-to-right cardiac shunt can ultimately produce severe pulmonary hypertension, as can an entity that has been called chronic pulmonary embolism. Schistosomiasis is the most common cause of unexplained pulmonary hypertension worldwide, although it is very rare in the United States. Collagen vascular disease is a fairly common cause of pulmonary hypertension, although it is not clear whether this represents a true vasculitis. Primary pulmonary hypertension is a diagnosis of exclusion and thus requires one to exclude all secondary causes.

The diagnosis of primary pulmonary hypertension can be made with relative certainty, however. The National Institutes of Health Registry of primary pulmonary hypertension, which was maintained from 1981 until 1987, enrolled over a five-year period 191 patients who met clinical criteria for primary pulmonary hypertension (1). In this series no patient was found on autopsy to have a secondary cause of pulmonary hypertension.

Diagnostic Testing for Pulmonary Hypertension

X-Ray. The first test in the evaluation of a patient with pulmonary hypertension should be a chest x-ray. Clear lung fields on the x-ray does not necessarily exclude parenchymal lung disease, as was reported by Carrington et al in 1960 (2). On the other hand, interstitial markings may be seen in pulmonary veno-occlusive disease, a subtype of primary pulmonary hypertension. Above all, one should insist on a good-quality upright posterior-anterior and lateral film. Portable x-rays are usually inadequate. If the radiograph of the patient reveals emphysema or interstitial lung disease, the diagnosis is established. However, if the chest x-ray reveals mild to moderate cardiomegaly with clear lung fields, virtually any of the other etiologies of pulmonary hypertension is a possibility (Table).

Functional Testing. Pulmonary function tests are essential to evaluate the presence of obstructive airways disease. People who smoke cigarettes do not necessarily have the chronic disorder, and documentation by pulmonary function testing is required. Keep in mind that sleep apnea is also an established cause of chronic pulmonary hypertension. Because the treatment of pulmonary hypertension arising from this entity is so different from the treatment of the disorder when it arises from any other cause, this etiology must be ruled out if the treating physician believes it to be a realistic clinical possibility. Pulmonary function tests in any patient with pulmonary hypertension will likely reveal a modest restrictive abnormality, which does not necessarily indicate restrictive lung disease. Data from the NIH Registry showed that total lung capaci-

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Adapted from the author's Grand Rounds in Medicine presentation on November 1, 1988 at the Mount Sinai Medical Center. From the Section of Cardiology, University of Illinois, Chicago, Illinois. Address reprint requests to the author, Chief of the Section of Cardiology, at University of Illinois Hospital, Box 6998 (M/C 787), Chicago, IL 60680.

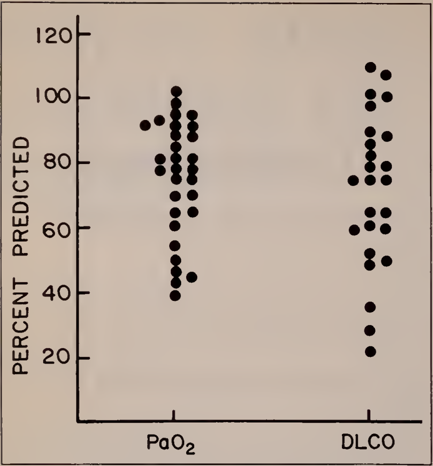


Fig. 1. Percentage of predicted normal values for arterial oxygen saturation at room air (PaO_2) and diffusing capacity for carbon monoxide (DLCO), 31 patients with primary pulmonary hypertension.

ty, forced vital capacity, and FEV_1 were reduced in patients with primary pulmonary hypertension as a secondary manifestation of high pulmonary artery pressure without any other evidence of restrictive lung disease (1). Airway flow, however, as represented by the FEV_1-FVC ratio, was normal. Consequently, to make the diagnosis of restrictive lung disease, one needs not only restrictive changes in pulmonary function testing, but other findings such as interstitial markings on the chest x-ray.

Arterial hypoxemia is ubiquitous in patients with primary pulmonary hypertension. At the University of Illinois we observed values as low as 30% of predicted for systemic arterial oxygen saturation, which reflects ventilation-perfusion mismatching magnified by a low cardiac output (Fig. 1). In some instances such low values may also represent right-to-left shunting from a patent foramen ovale. Diffusing capacity for carbon monoxide is also quite variable and is often abnormal, although it does not correlate with the severity or the etiology of the pulmonary hypertension.

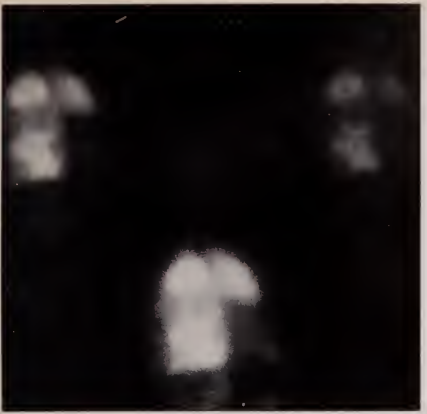
The perfusion lung scan has proved to be a very informative test in patients with pulmonary hypertension, because the absence of a history suggesting pulmonary embolic disease need not rule out disease. And a scan may also offer insight into the pathology of the pulmonary vascular disease. Several published series have shown that, although lung scans from patients with primary pulmonary hypertension are often abnormal, such patients can be reliably distinguished via the scan from those with thromboembolic disease. The presence of any segmental or subsegmental perfusion defect should raise the possibility that pulmonary thromboembolism is present.

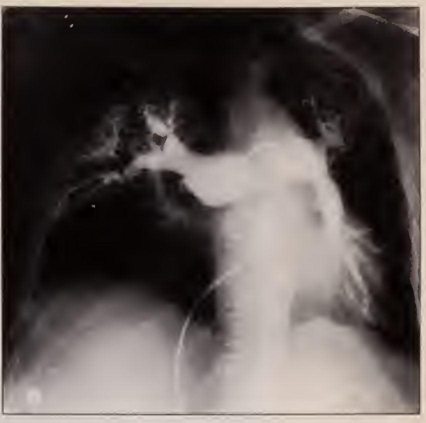
The pulmonary angiogram is essential for a patient with an abnormal lung scan that suggests the possibility of thromboembolic disease. It should be performed selectively based on the pattern of the perfusion lung scan. There is considerable concern about the risk that is associated with pulmonary angiography in the patient with primary pulmonary hypertension. But, although the majority of fatalities during pulmonary angiography reported in the literature have occurred in patients with severe pulmonary hypertension, adequate precautions appear to reduce the risk to acceptable levels. We at the University of Illinois advocate constant systemic arterial blood pressure monitoring, and administer 1 mg of atropine at any sign of increased vagal tone. It is our impression that a large proportion of the cardiac arrests that occur during pulmonary angiography are vagally mediated and thus can be prevented by the preadministration of atropine. In the NIH Registry we documented 50 pulmonary angiograms performed in patients with primary pulmonary hypertension without one serious adverse consequence.

Illustrative Case Report: Chronic Thrombotic Obstruction. To illustrate the importance of these suggestions I present the case of a patient referred to me in 1983 with a diagnosis of primary pulmonary hypertension. She was a former resident of New York who had moved to a southern suburb of Chicago. At that time she was extraordinarily ill, functional class IV, and dependent on an oxygen tank and wheelchair.

Her chest x-ray revealed mild cardiomegaly with large central pulmonary arteries and clear lung fields. We performed a perfusion lung scan that showed anatomic defects suggesting a lobar perfusion defect in her right lower lobe and left middle lung field (Fig. 2). To investigate this possibility, we performed a pulmonary angiogram. That study revealed a large pulmonary artery consistent with pulmonary hypertension, but the absence of a blood vessel going to the right lower lung field and one to the left middle lung field (Fig. 3).

The unusual appearance of this pulmonary angiogram was interpreted by our radiologist as congenital absence of the pulmonary artery to





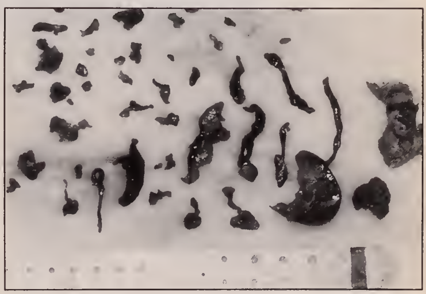


Fig. 2. **Above left** Patient with thrombotic obstruction of pulmonary arteries initially diagnosed as having primary pulmonary hypertension. Perfusion lung scan, left posterior oblique erect view. **Fig. 3. Above right** Same patient. Pulmonary angiogram. Absence of vessels to right lower lobe and left middle lung reveal thrombus as underlying problem. **Fig. 4. Right** Same patient. Arterial thromboembolism removed. Patient made an uneventful recovery and within 6 months became symptom free.

the right lower lobe and left middle lung. It was my impression, however, that the patient had proximal pulmonary thromboembolism. I approached our surgeon and asked him to perform a pulmonary endarterectomy based on these findings. Although the surgeon was initially skeptical, he agreed, and when the patient was operated on, an enormous amount of pulmonary thrombus was removed from the large pulmonary arteries (Fig. 4). Her disorder was not acute pulmonary embolism, but long-standing, well-endothelialized clots.

Differential Diagnosis of Chronic Obstruction of Proximal Arteries. This entity—chronic thrombotic obstruction of the proximal pulmonary arteries—is probably less common than primary pulmonary hypertension and probably more often misdiagnosed. In the Cardiology Section at the University of Illinois, we have now seen many patients with this entity who were diagnosed as having primary pulmonary hypertension. The mechanism is unclear; it does not appear to be recurrent thromboembolism, but may represent an initial occult pulmonary embolism which goes either undetected or untreated. Possibly the clot does not become lysed normally, but rather results in a persistent pulmonary vascular occlusion that predisposes to procoagulant changes in the pulmonary arteries and subsequent retrograde thrombosis. This sequence of events would explain why the patients do not initially seem to have, or to report, recurrent pulmonary embolism, but rather insidious onset of chronic pulmonary hypertension.

The interpretation is also supported by the report of Riedel et al (3) of a series of patients serially catheterized and studied over a two-year period. He grouped the patients into four categories. The first group included patients with an acute pulmonary embolism of the clinical variety commonly seen. The mean pulmonary artery pressures in this group were normal initially and

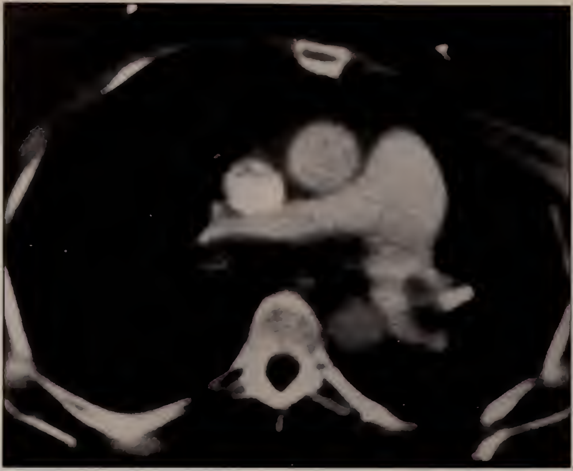


Fig. 5. Ultrafast CT scan, patient with proximal thromboembolism. Pulmonary angiogram suggested normal right pulmonary artery, whereas CT scan revealed laminated thrombus in markedly dilated pulmonary artery.

normal on restudy two years later. It is not well appreciated that the unconditioned right ventricle cannot generate pressures of severe pulmonary hypertension, so that in a patient with an acute pulmonary embolism, severe pulmonary hypertension will not occur unless there is some underlying cardiopulmonary disease.

The second group, categorized as "subacute pulmonary embolism," included patients who gave a history of pulmonary embolism within the previous month. Riedel et al also noted that pulmonary artery pressures were normal at baseline and unchanged two years later.

The third group, categorized as "recurrent pulmonary embolism," included patients who initially had clinical pulmonary embolism and were treated with anticoagulant therapy, which was discontinued after six months. At some further date each had another acute pulmonary embolism, and on recatheterization also had normal pulmonary artery pressures.

The fourth group was categorized as "occult pulmonary thromboembolism." In this group the patients did not initially have an acute pulmonary embolism, but pulmonary hypertension and an abnormal lung scan. They had severe elevations in pulmonary artery pressure at baseline and, when placed on anticoagulant therapy and restudied two years later, had similar elevations in pulmonary artery pressure. It is that group that probably represents the entity of chronic thrombotic obstruction of the proximal pulmonary arteries.

Angioscopy and Ultrafast CT Scans to Document Proximal Extent. Researchers at the University of California in San Diego have reported on a series of these patients and have observed that angioscopy is a diagnostic tool helpful in documenting the proximal extent of the pulmonary thromboembolism (4). If the embolism is distal to the lobar vessels it is likely to be inoperable. Lung scans generally underestimate the amount of clot compared to pulmonary angiograms, and pulmonary angiograms themselves often underestimate the proximal extent of the clot as well. At the University of Illinois we perform ultrafast computed-tomographic studies in which we are able to get high-resolution images. These CT scans show proximal filling defects more often than do pulmonary angiograms, and CT scans are also considerably less invasive than angiograms (Fig. 5). Consequently we find these scans to be an essential test in the preoperative assessment of the patient.

Echo-Doppler Studies for Unexplained Pulmonary Hypertension. In diagnostic studies of the patient with unexplained pulmonary hypertension echo-Doppler studies have been quite helpful for evaluating the presence of valvular and myocardial disease and for assessing congenital heart disease that may have been missed by history or physical examination. In addition, echo-Doppler studies afford insight into the severity of the pulmonary vascular disease. The typical two-dimensioned echocardiogram of these patients shows a right ventricle that is markedly enlarged, with an enlarged right atrium. The left ventricle looks compressed, but in actuality it is probably not. Patients with severe cardiomyopathies can have very large right and left ventricles. In primary pulmonary hypertension it is more likely that the left ventricle is chronically underfilled, as in mitral stenosis, and the septal architecture is distorted because of the presence of severe pulmonary hypertension. My group has reported that the left ventricular internal dimension on M mode, or left ventricular cavity area, as well as the reversed septal curvature, correlates much better with the level of pulmonary vascular resistance than with the size or shape of the right ventricle (1).

Cardiac Catheterization. Finally, cardiac catheterization is essential in order to exclude congenital heart disease and assess pulmonary wedge pressure. Another myth in evaluation of patients with pulmonary hypertension is that one cannot get accurate wedge pressure tracings. In over 100 patients with pulmonary hypertension I have studied, each patient who had an elevated wedge pressure had either high filling pressures in the left ventricle, or occult mitral stenosis. The caveat is that the people who perform the catheterization study must be persistent and take their time in sampling multiple areas of the lungs to obtain accurate wedge pressure tracings.

Primary Pulmonary Hypertension

In the 1940s and 1950s Paul Wood, the famous British cardiologist, observed that primary pulmonary hypertension follows a rapid downhill course that leads to death within two years in the majority of cases. The data from the NIH Registry show that patients who are New York Heart Association functional class III have a median survival of about three years, but those who are functional class IV have a median survival of only about six months. The overall survival of patients in the NIH Registry was 2½ years, similar to Dr. Wood's projection. This makes the prognosis of patients with primary pulmonary hypertension worse than for most cancers and worse than AIDS.

Data from the Registry also confirmed that the highest prevalence of primary pulmonary hypertension occurred in people who were in their 20s and 30s, with a female-to-male ratio of approximately 1.7 to 1. Some people, however, were diagnosed when they were over 60 years of age.

Importance—and Difficulty—of Early Diagnosis. One of the major difficulties in making an early diagnosis of primary pulmonary hypertension is that the first symptom, which is usually dyspnea, is actually a symptom of normal life. Sixty percent of the patients in the Registry reported that dyspnea was their initial symptom, and virtually all of them reported having dyspnea by the time the diagnosis was made. The average time from the onset of the first symptom until the diagnosis was made, however, was over two years; for some people the diagnosis was not made until ten or more years after onset. When the patient has fairly advanced disease, little in the way of treatment is possible.

Histologic Subtypes. In 1973 the World Health Organization classified primary pulmonary hypertension into three histologic subtypes (5): plexogenic pulmonary arteriopathy; pulmonary microembolism, which we now call thrombotic pulmonary arteriopathy; and pulmonary veno-occlusive disease (Table).

The histologic characteristic of plexogenic

TABLE
Histologic and Clinical Subtypes of Primary Pulmonary Hypertension

	Clinical characteristics†		
WHO histologic subtypes*	Lung scan	Chest x-ray	Demographics
Plexogenic pulmonary hypertension	normal, evenly distributed tracer	clear lung fields	younger women
Thrombotic pulmonary arteriopathy	motheaten, diffusely patchy	clear lung fields	equal M:F older ages
Pulmonary veno-occlusive disease	abnormal tracer distribution	hazy lung fields increased interstitial marking as in mitral stenosis	too small to characterize

* Adapted from ref. 5.
† At The University of Illinois.

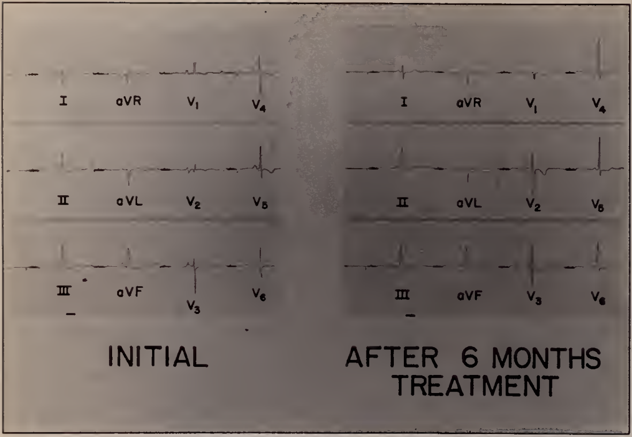


Fig. 6. Initial EKG from a patient with primary pulmonary hypertension reveals right axis deviation and voltage changes of right hypertrophy. In follow-up EKG 6 months later, axis has shifted to normal and all anterior right ventricular forces in precordial leads are reduced, indicating resolution of RVH. Patient had excellent clinical response with complete resolution of her symptoms.

pulmonary arteriopathy is concentric laminar intimal fibrosis, often with total occlusion of the vascular lumen. It is likely that some abnormality in the pulmonary vascular endothelium causes a change in the mediators of vascular smooth muscle, which results in vasoconstriction and an elevation in the pulmonary arterial pressure. The most advanced lesion is known as the plexiform lesion, which looks somewhat like a glomerulus in the small arteriolar bed.

Patients with thrombotic pulmonary arteriopathy often show evidence of recanalized pulmonary thromboembolism appearing as a vascular web. The mechanism in these patients is also probably endothelial cell injury, with eccentric intimal proliferation which leads to a reduction in the vascular lumen and subsequent medial hypertrophy, as well as vascular occlusion from the pulmonary thrombus.

Pulmonary veno-occlusive disease, the least common of all of the entities, is the least understood; it accounts for less than 10% of all patients. Its histologic characteristics are fibrosis and thrombosis of the pulmonary venules with secondary intimal proliferation and medial hypertrophy, which can extend back to the arteriolar bed as well. A clinical observation made years ago (6) was that patients with pulmonary veno-occlusive disease can have a chest x-ray pattern showing interstitial markings similar to mitral stenosis.

At the University of Illinois we have also observed two predominant types of lung-scan patterns in patients with primary pulmonary hypertension: a normal pattern of relatively even distribution of tracer, and a moth-eaten, diffusely patchy pattern (6). The original notion was that the normal pattern represents early disease and the patchy pattern late disease. However, we followed up patients with serial lung scans over years and found that patients whose lung scans were initially normal had normal lung scans until their death, whereas patients with patchy scans had patchy scans which never changed.

When we looked at the chest x-ray patterns and lung scans of patients with primary pulmonary hypotension and compared them to the histologic studies, we were able to identify clinical grounds for the three WHO histologic categories (6) (Table). This clinical grounding allows noninvasive characterization of the histologic patterns of patients with primary pulmonary hypertension.

When we reviewed the experience at the University of Illinois, we noted that patients with plexogenic arteriopathy are generally younger and women, whereas those with thrombotic arteriopathy are more equally distributed between men and women of a slightly older age group. The number of patients with veno-occlusive disease is too small to make demographic statements.

Some data suggest that pulmonary embolism is highly unlikely as a cause of primary pulmonary hypertension. A retrospective study by Fuster et al at the Mayo Clinic noted that patients diagnosed as having primary pulmonary hypertension who received coumadin anticoagulant

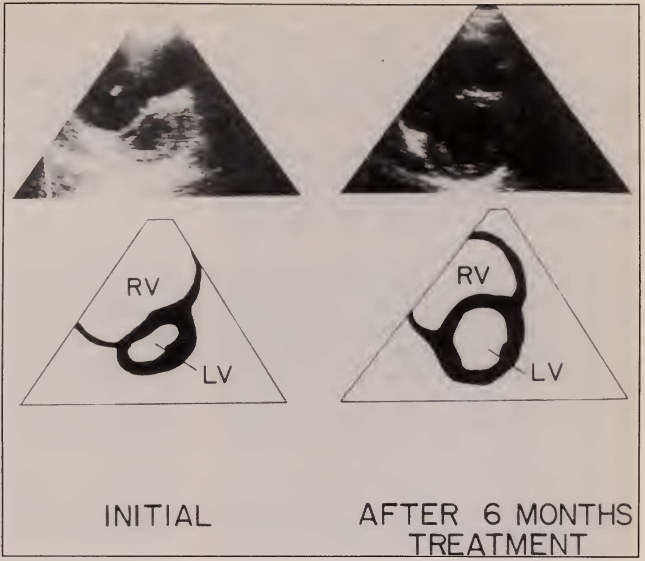


Fig. 7. Same patient as in Fig. 6. Initial two-dimensional echocardiogram freeze-framed in parasternal short axis view reveals markedly enlarged right ventricle, distorted septal curve, and small left ventricle. In follow-up echocardiogram six months later, this patient's left ventricular architecture is normal and right ventricular size is markedly reduced.

therapy had a higher rate of survival than those patients with proven embolism (7). Yet animal studies suggest that more than 90,000 microemboli would be necessary to raise the pulmonary artery pressure by just 5–10 mm Hg (8). Eisenberg et al recently measured fibrinopeptide A levels in patients with primary pulmonary hypertension and found very elevated levels suggesting that in situ thrombosis of the pulmonary bed was occurring in these patients (9). These additional data support the view that long-term anticoagulation is worthwhile treatment for patients with primary pulmonary hypertension.

Aggressive Treatment of Pulmonary Hypertension Using Vasodilators

In 1976 a case report of a patient with primary pulmonary hypertension appeared in the *New England Journal of Medicine* in which the investigators noted that the pulmonary vascular resistance fell after an infusion of isoproterenol and consequently the patient was treated with long-term sublingual isoproterenol tablets (10). Unfortunately, because of its short half-life, this drug had to be taken every two hours, making it somewhat impractical in therapy. As other investigators used isoproterenol, however, it became apparent that this agent might not be effective (11).

Diazoxide was then becoming popular as an effective treatment of severe essential hypertension. A report describing the effect of that agent on three patients with primary pulmonary hypertension suggested that it might be useful (12). However, as more investigators used that drug, it became apparent that diazoxide was not only ineffective, but hazardous as well; in fact, several deaths have been attributed to it (13). From my standpoint I would say that diazoxide is not contraindicated for patients with primary pulmonary hypertension.

In 1980 Rubin and Peter reported their experience with four patients using oral hydralazine as treatment for the disorder (14). They noted that acutely, and after three months, the pulmonary vascular resistance was reduced with hydralazine. Shortly afterward, however, Packer et al reported adverse effects of hydralazine in patients with primary pulmonary hypertension (15).

A case report on the effectiveness of phentolamine appeared shortly afterward in the *Annals of Internal Medicine,* only to be followed by an additional case report of its adverse effects (16, 17). And more recently, a report by Rubin et al on the use of nifedipine in patients with the primary disorder showed that that agent lowered pulmonary vascular resistance and improved right ventricular performance (18). However, the calcium blockers as a group have also been reported to be harmful (19).

During this period I was rather skeptical of the effectiveness of vasodilators in primary pulmonary hypertension because of the lack of documentation of clinical benefits. One must understand that it has been very difficult to lower the pulmonary pressure in these patients and consequently physicians focused more on lowering the pulmonary vascular resistance. The pulmonary vascular resistance cannot be measured directly; it is calculated as a hydraulic equivalent to Ohm's law—the mean pulmonary pressure, less the wedge pressure, is divided by the cardiac output. Thus, the pulmonary resistance can be lowered without lowering pulmonary pressure simply by increasing cardiac output.

One of my earlier patients with primary hypertension, in the pre-1980 era, was challenged with tolazoline, isoproterenol, and hydralazine. The patient's pulmonary vascular resistance fell with all three drugs because the cardiac output went up with all three drugs. However, isoproterenol increased rather than lowered the pulmonary artery pressure. It would be inappropriate to treat a person with primary hypertension with a drug that lowered pulmonary resistance if at the same time the drug raised pulmonary pressure. Although both hydralazine and tolazoline also lowered the patient's pulmonary resistance, only tolazoline lowered pulmonary artery pressure.

In a 1983 review, I reported with colleagues on published reports of the change in pulmonary pressure following vasodilator challenges of patients with pulmonary hypertension (20). The vasodilators have been developed as systemic agents, and it is apparent that they typically produce a substantial reduction in systemic arterial pressure. It was also apparent, however, that these drugs rarely effected any reduction in pulmonary artery pressure.

We then decided to test our clinical hypothesis and evaluated the response of 23 consecutive patients referred with primary pulmonary hypertension to the acute administration of either hydralazine or nifedipine (21). A 20% reduction in pulmonary vascular resistance was considered a favorable response for this pilot trial. The pulmonary resistance of five of these patients was not lowered even 20%, and their clinical course was quite poor. However, 18 of the 23 patients did respond acutely with lowered pulmonary resistance. Half of them were treated with the most effective drug, and over time we found that some patients got better, some got worse, and some stayed the same. The other half of the patients were not treated with a vasodilator, and again we observed that some patients got better, some got worse, and some stayed the same. When we plotted their survival over a two-year time period using Kaplan-Meier estimates, it was apparent that the patients who had an acute reduction in pulmonary resistance from vasodilator challenge did better than those who did not, but neither treatment nor nontreatment altered their survival.

Using the premise that a reduction in pulmonary pressure is essential for sustained clinical improvement, we then developed a protocol that has been referred to as "high-dose calcium channel blocker therapy." It is probably more appropriately termed "optimal-dose therapy" (22). In our present protocol, we give patients hourly doses of 20 mg nifedipine (or 60 mg diltiazem) either until their systemic blood pressure falls (in which case they cannot tolerate it), or until they have other adverse effects to the drug, or until we obtain a substantial reduction in pulmonary artery pressure. Conventional doses produce little change in pulmonary artery pressure and resistance in many patients; for these patients a considerably higher dose of calcium blockers is necessary before we at the University of Illinois observe a marked reduction in mean pulmonary artery pressure commensurate with an increase in cardiac output. We then calculate half of the total cumulative dose, to be given to the patients every 6–8 hours.

In our initial series of 13 patients, 8 of the patients had a beneficial response as manifest by a substantial reduction in both pulmonary pressure and pulmonary vascular resistance. Before we decided to report our findings, however, we wanted to make sure that the changes we observed were truly beneficial to the patient. Consequently we waited until we had long-term results, which we defined as one-year follow-up. From the Registry experience it is apparent that at least a third of these patients should have been dead after one year.

Serial electrocardiograms (Fig. 6) and echocardiograms (Fig. 7) show the improvements that took place in six months. When these patients were restudied at the end of one year, we observed that the reduction in mean pulmonary artery pressure and pulmonary vascular resistance achieved after the initial 24 hours of high-dose calcium blocker therapy was sustained over the one year as well. One patient whose values reverted toward her original values did not take the recommended high-dose calcium blocker medication because of some concern by her referring physician. The lesson we learned from this is that the optimal dose of drug is essential for sustained clinical improvement.

Summary

In the last decade we have made great strides in our understanding of the clinical presentation and findings, natural history, and treatment of patients with primary pulmonary hypertension. Recognizing the tendency for in situ thrombosis in many of these patients now gives strong support to the recommendation that anticoagulants be used for patients who are felt to have underlying pulmonary artery thrombosis. Vasodilators in adequate doses can be demonstrated to cause substantial reductions in pulmonary artery pressure and pulmonary vascular resistance which causes regression in right ventricular hypertrophy and marked clinical improvement. There is still much to be accomplished in this field: a major challenge is to diagnose pulmonary hypertension in patients earlier, at a more treatable stage, and to develop effective treatments for patients with severe right ventricular dysfunction refractory to vasodilator treatment.

Questions and Answers

Richard Gorlin: Thank you very much, Dr. Rich. That's among the more encouraging things that one has heard about this devastating disease. Let me ask you two questions. Do you see any role for a biopsy of the lung in patients like this, to try to get some idea of the pathology of the arterioles? Does that help you at all?

Rich: I would say no. It was our initial practice to perform an open-lung biopsy on all of our patients. We wanted to make sure that we had an accurate diagnosis and that we were not missing a secondary disease. As it has turned out, in our experience and the experience reported by the Registry, none of the patients who met the clinical criteria for primary pulmonary hypertension showed—in biopsy or autopsy—a disease other than primary pulmonary hypertension of one of the three histologic subtypes. There was not one patient. As for knowing the stage of the disease, knowing the severity of the vascular changes, no one really knows if that will tell you whether the patient will respond to treatment. But given the morbidity of open-lung biopsy, I would rather challenge these patients with medications to find out their vascular responsiveness. At present we no longer advocate open-lung biopsy for these patients.

Gorlin: Is there no differentiation, whether you find plexogenic or veno-occlusive or thrombotic disease, between who will respond and who will not?

Rich: We are starting to analyze our data at the University of Illinois, and our experience now encompasses more than 60 patients with primary pulmonary hypertension who have undergone this high-dose calcium blocker challenge. It appears that patients with both thrombotic arteriopathy and plexogenic arteriopathy, based on lung scan pattern, have equal opportunity to respond to calcium blockers. With veno-occlusive disease, however, we had two patients who went into pulmonary edema following vasodilator challenge. This suggests that perhaps the increased preload due to an increased cardiac output could not be handled because of the venous obstruction, and thus we consider calcium blockers contraindicated in those patients.

Milton Packer: I think that we've had some problem with the calcium channel blockers at high doses. We do have very little to explain the results of vasodilator therapy, in trying to figure out why vasodilators work in primary pulmonary hypertension. A large percentage of these patients have thrombotic occlusive disease as the cause of the elevated pulmonary pressure. Except for the fact that the histology is somewhat similar in the plexogenic and thrombotic patients, is there any reason why vasodilators should work?

Rich: Certainly the plexogenic group reflects a spectrum of involvement of vessels—not all the pulmonary arterioles are affected equally. Some patients will have mild degrees of medial hypertrophy without any detectable intimal proliferation. Thus, there is reason to believe in some potential for a vasodilator response in those vessels. Patients with thrombotic arteriopathy may be somewhat less responsive than patients with plexogenic arteriopathy, but again there is a spectrum of involvement of the pulmonary vessels. Thus, I really do not find the fact that vasodilators are effective in some of these patients at all surprising. I share with you, however, that I did not focus on the hazards of calcium blocker treatment. The calcium blocker drugs have negative inotropic properties, and we are reluctant to employ even conventional dosages in patients who come to us with overt right heart failure (ascites, leg edema, high right atrial pressures, and low cardiac outputs); this group falls into the group of nonresponders. These are the patients we feel can get into serious trouble with drug-induced heart failure. The patients who have preservation of right ventricle function with low right ventricular end-diastolic pressure, even though they generate high systolic pressures, have a reasonable chance to respond.

Gorlin: Can you localize by your hemodynamics the level in the vascular system at which there is a response? Is it the left ventricle, pulmonary veins, capillaries, or small arteries of the lungs?

Rich: In a sense, in the patients who are responders it is all of the above. The left ventricle is relatively stiff due to the distorted septal architecture. Left ventricular end diastolic pressure is not normal, but is slightly increased in this group, and as the patients' disease becomes more advanced it rises even higher. Filling characteristics of the left ventricle, however, will return to normal with treatment. We've shown with Doppler studies that there is abnormal left ventricular filling in patients with primary pulmonary hypertension, with a marked dependency on atrial systole for ventricular filling. That pattern reverses with successful vasodilator therapy.

There has never been a patient with primary pulmonary hypertension and atrial fibrillation described. I believe the reason is that the two are incompatible. These patients are so dependent on atrial systole that should they have an episode of atrial fibrilation they may not survive. It is well known that sudden death is one of the causes of death in this group, and that may be one explanation for this.

But left ventricular diastolic function can improve with vasodilator therapy, pulmonary blood flow will improve, right ventricular architecture improves, and thus their entire cardiopulmonary system is returned more toward normal. Many of my patients are now leading symptom-free lives. Questions I often get now are "Is it OK to ski?" or "May I play hockey?"

Marvin Levitt: What do you do about the salt and water retention of these people? Particularly if they have high blood pressure? When we have to dialyze patients with primary pulmonary hypertension to take fluid out we have a terrible problem. How do you manage these patients who become edematous?

Rich: In the typical patient with pulmonary hypertension we are generous with the use of diuretics. Because they seem to have increased lung water, even though their pulmonary wedge pressures are minimally elevated, they feel much better with relief of their symptoms of dyspnea. I also believe that right ventricular wall stress will go down if one reduces some of the intravascular volume. The problem to which I think you are referring is the patient who needs high filling pressures in the left ventricle that is reduced with diuretics. In that respect, they behave more like the hypertensive heart disease patient who has high left ventricular end-diastolic pressure, and if on dialysis it is brought too low, they become hypotensive, whereas if they are not dialyzed enough they develop pulmonary edema. This has not been a common problem for us in the patients with primary hypertension, but we have seen it on occasion. It is my practice to use diuretic therapy in proportion to the patient's symptoms. Orthopnea can be a symptom of severe pulmonary hypertension, and diuretic treatment will improve that as well.

Richard Stein: Is it possible to view this disease conceptually as a vasospastic disease in the lung? So that in patients who are responding, vasospasm is a dominant feature, and as the disease progresses, the lung vasculature responds in an analogous fashion to the systemic vasculature in hypertension? Do they get progressively more sclerotic and eventually thrombose the pulmonary vessels in response to the high pressure? Is the responding patient the one with the earlier vasospastic disease?

Rich: If I can editorialize and hypothesize about the etiology of hypertension, I believe it rests in the endothelial cell, and what we are seeing is two responses of the pulmonary endothelium to injury. That is, one response is the establishment of a procoagulant state from endothelial injury which leads to in vivo thrombosis, eccentric intimal fibrosis, and so on. The other response is an effective loss of endothelial-derived relaxing factors, also as a result of endothelial injury, which results in pulmonary arterial vasoconstriction.

What makes a unified hypothesis very probable is experience in congenital heart disease: patients will develop pulmonary hypertension (Eisenmenger's syndrome) with plexogenic arteropathy if the shunt is due to a ventricular septal defect, whereas patients with atrial septal defects are less likely to develop pulmonary hypertension, but still have increased pulmonary blood flow due to their congenital left-to-right shunt. Most of these people develop a thrombotic arteriopathy. There must be something in the nature of the increased pulmonary blood flow that affects the endothelium and the way it responds.

You are right, however, in that once medial hypertrophy occurs, secondary intimal changes may also occur. On the other hand, it is interesting that with mitral stenosis, a classic example of secondary pulmonary hypertension, one can also have marked hypertrophy of the media and some intimal changes, but generally the intimal response is much less. This is a reversible form of pulmonary hypertension and almost always improves with surgical replacement of the mitral valve. In fact, pulmonary hypertension of any severity is not a contraindication for mitral valve replacement for mitral stenosis.

Fernando Elijovich: The antidiuretic hormone vasopressin is a powerful dilator of the pulmonary vasculature, particularly in experimental models of hypoxemic pulmonary vasoconstriction. Are you aware of any reported attempt at treating primary pulmonary hypertension with this hormone?

Rich: I have not seen any clinical work on vasopressin. There is some work appearing with atrial naturetic factor, which seems to have mild to modest effects on pulmonary hypertension. Prostacyclin, when given in very large doses, will cause pulmonary vasodilation, but causes systemic vasodilation as well. We are looking at every possible avenue for therapy. Keep in mind, though, that the changes that occur from hypoxic lung disease are quite different from those in primary pulmonary hypertension. Hypoxic lung disease causes hypertrophy of a much smaller pulmonary artery vessel, and a considerably increased amount of elastin and fibrous tissue, with an actual loss of vascular beds.

If I can leave you with one last thought, it is that the treatment of pulmonary hypertension should really focus on the etiology. To date, vasodilators have only been shown to be effective in the group of patients with primary pulmonary hypertension. I am still, as is Dr. Packer, skeptical that in patients with secondary pulmonary hypertension, be it from collagen vascular disease or hypoxic lung disease, vasodilators have had any significant impact. In my opinion there is not yet a convincing published report.

Gorlin: Thank you very much, Dr. Rich.

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Grand Rounds

Saving Lives after Myocardial Infarction:

The Role of Beta-Adrenergic Blockers

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Despite a decline in the incidence of coronary heart disease in the United States, more than 600,000 patients are admitted to hospitals annually with a diagnosis of acute myocardial infarction (MI) (1). For patients having their first infarction, there is a 15% in-hospital mortality; the figure is higher for patients with recurrent infarctions (2). On discharge from the hospital, patients continue to have an increased risk of cardiovascular morbidity and mortality. Patients under 70 years of age who survive the in-hospital phase of MI have a 10% mortality rate in the first year after discharge, the highest proportion of deaths occurring in the first three months (2). Subsequently, there is a 5% annual mortality rate, six times higher than the expected rate in an age-matched population without coronary disease (2). Approximately 85% of deaths that occur after hospital discharge are related to coronary artery disease, and almost half are sudden deaths. Ventricular fibrillation appears to be the primary cause of sudden death.

Prospective epidemiologic studies have identified subsets of infarct patients with a high, intermediate, or low risk of mortality (3, 4). Prolonging life in this heterogeneous group of patients is a major goal of preventive therapy. To reach this goal, a variety of therapeutic approaches have been evaluated, including lifestyle measures (dietary modification, cessation of smoking, physical exercise) and coronary artery reconstructive procedures (5). Specific pharmacologic agents have included anticoagulants, thrombolytic drugs, drugs that inhibit platelet aggregation, antiarrhythmic drugs, angiotensin-converting enzyme inhibitors, calcium-entry blockers, and β-adrenergic blockers (5). The calcium-entry blockers and β-adrenergic blockers have always appeared attractive as preventive measures because of their anti-ischemic, antiarrhythmic, and antihypertensive actions (6); aspirin has been favored because of its antithrombotic activity (7). In this article, the clinical use of β-adrenergic blockers for patients with MI is discussed.

Beta-Adrenergic Blockade

β-Adrenergic blockers have been proven safe and effective for the treatment of patients with various cardiovascular disorders (8). Since 1965 they have been considered as possible therapies for extending life in patients surviving MI (5). On the basis of multiple long-term clinical studies, the efficacy of β-blockers in reducing the risk of mortality and nonfatal reinfarction in survivors of an acute MI has been proven (5, 9). They also have been shown to reduce the extent of myocardial injury and mortality during the acute phase of MI (5). Finally, β-blockers have been suggested for the primary prevention of MI and death in patients with hypertension, stable angina, and unstable angina; their protective effects in these conditions, however, are less well defined (10).

Long-Term Reduction of Cardiovascular Mortality Risk in Survivors of Acute Infarction

The presumed major mechanisms for increased risk of cardiovascular mortality during the postinfarction period include persistent myocardial ischemia, cardiac arrhythmias, and left ventricular (LV) dysfunction (1–5, 10).

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TABLE 1

Pharmacologic Properties of β-Adrenoceptor Blocking Drugs Tested in Long-Term Trials

Drug	Relative β_1-selectivity	Intrinsic sympathomimetic activity	Membrane stabilizing activity
Alprenolol*	0	+	+
Atenolol	+	0	0
Metoprolol	+	0	0
Oxprenolol*	0	+	+
Pindolol	0	+ +	0
Practolol*	+	+	0
Propranolol	0	0	+ +
Sotalol*	0	0	0
Timolol	0	0	0

* Not available for clinical use in the United States

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Elevations in plasma catecholamine levels or enhanced sympathetic drive can increase both the severity of myocardial ischemia and the frequency of ventricular arrhythmias. After the clinical introduction of propranolol for therapy of angina pectoris and arrhythmias, it was proposed that a β-blocker might favorably influence the natural history of patients with MI by attenuating the undesirable consequences due to increased sympathetic nervous system activity (5, 10, 11). Depression of LV function, the other major risk factor contributing to mortality after infarction, can be caused by β-blockade (8, 11). For this reason, β-blockers were initially avoided or used in small doses in patients with MI. Only in the past 15 years have the results of long-term studies demonstrated the benefit of β-blockade in reducing total mortality and nonfatal reinfarction (5, 9, 10).

Long-Term Beta-Blocker Prevention Trials

Since 1974, 14 major randomized controlled trials with β-blockers after acute MI have been reported, in which treatment and mean followup extended from nine months to six years (12–31). Over 18,000 survivors of acute MI were studied in an attempt to document reductions in total mortality, cardiovascular mortality, coronary mortality, sudden death, and nonfatal reinfarction. Eight different β-blockers have been evaluated in these studies (12–31): alprenolol, metoprolol, oxprenolol, pindolol, practolol, propranolol, sotalol, and timolol (Table 1).

The 14 trials met the following criteria for study design: a trial endpoint of total mortality or a clearly defined cause-specific mortality, a total sample size of at least 200, and random assignment of patients to either the β-blocker group or a concurrently followed control group. The study populations contained from 230 to 3,837 patients (12–31). Thirteen of the 14 trials used a placebo-treated control group and had a double-blind phase. The time between the infarction and the start of β-blocker or placebo treatment ranged from under 24 hours to 7.5 years. In 12 trials, patients in the low- and intermediate-risk groups were studied predominantly (12–14, 16–19, 24–31), and in two trials only high-risk patients were evaluated (15, 23).

The results from 11 of the 14 long-term trials showed a lower mortality rate in the β-blocker group than in the placebo group (Table 2) (12–15, 17, 18, 23–25, 27–31). In the three large studies, the reduction in mortality with β-blockade was statistically significant (18, 24, 27, 28). In the remaining eight trials, the results were not conclusive with regard to overall mortality.

Combining the results of all 14 β-blocker trials, mortality was reduced by approximately 21%. Caution is advised in interpreting such results from pooled data because of the inherent differences among the studies in patient population, type and dosage of β-blocker, and time of initiation and duration of treatment (5, 9, 10, 21).

Nine of the 10 trials reporting on the incidence of nonfatal reinfarction showed lower rates in the actively treated groups (5, 10). In only one of the trials was this lower incidence statistically significant. A comparison of the effect of treatment on the incidence of nonfatal reinfarction is complicated for many reasons. The diagnostic criteria for infarction differed among the trials, for example, resulting in large differences in incidence. A statistical test for homogeneity, however, indicated that the result of each trial was consistent with that of the other trial it was tested against. When all the findings from the nine placebo-controlled, double-blind trials are pooled, the reduction in nonfatal reinfarction is 22%, a benefit almost identical to that for overall mortality.

Possible Mechanisms of Benefit

Anti-Arrhythmic Effects. An analysis of cause-specific mortality in the β-blocker trials indicates that the reductions in total mortality were caused by a reduction in cardiovascular-caused deaths (5, 10). Although different definitions of "sudden death" were reported in the

TABLE 2

Results of Long-Term (more than 9 Months) β-Blocker Trials

	No. of Patients		Mortality (%)		
Trial (ref. no.)	Control	Randomized intervention	Control	Intervention	p*
Wilhelmsson et al (31)	116	114	12.1	6.1	0.18
Ahlmark et al (12)†	93	69	11.8	7.2	0.48
Barber et al (17)‡	147	151	31.3	27.2	0.51
Multicentre International Study (28)	1520	1533	8.2	6.3	0.051
Andersen et al (14)‡	242	238	26.2	25.2	0.92
Baber et al (16)	365	355	7.4	7.9	0.91
Norwegian Multicenter Study (27)	939	945	16.2	10.4	0.0003
BHAT (18)	1921	1916	9.8	7.2	0.005
Hansteen et al (23)	282	278	13.1	9.0	0.16
Julian et al (25)	583	873	8.9	7.3	0.32
Taylor et al (29)	471	632	10.2	9.5	0.78
Pindolol Study Group (15)	266	263	17.7	17.1	0.36
European Infarction Study (19)	880	861	5.1	6.6	0.14
Lopressor Infarction Trial (26)	1200	1195	5.2	5.5	0.90

* p values computed for χ^2 test comparing the proportion of deaths in each group.

† Incomplete reporting.

‡ Mortality includes all in-hospital deaths.

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trials, a large part of the benefit from β-blocker therapy appears to have stemmed from the prevention of these deaths (5, 10, 20). Seven trials reported on sudden death; the rates of sudden cardiac death were lower in the β-blocker group for all seven trials (Table 3) (20).

β-Blocker treatment appears to manifest a trend toward a greater overall reduction in sudden cardiac death than in all-cause mortality. The weighted-risk ratios for sudden cardiac death vary between 0.15 to 0.84 (mean 0.67), indicating an overall reduction of 33% in sudden cardiac death. Indeed, if sudden cardiac deaths are subtracted from all-cause mortality, the remaining death rate is 3.5% in the intervention group and 4.4% in the control group, which represents an intervention:control risk ratio of nonsudden death of 0.8. Thus, although nonsudden deaths

TABLE 3

Selected Mortality Results from Long-Term β-Blocker Trials

	Patients randomized		All-cause mortality			Sudden cardiac death			
Trial (ref. no.)	I (no.)	C (no.)	I (%)	C (%)	RR I:C (%)	D (hr)	I (%)	C (%)	RR I:C (%)
Wilhelmsson et al (31)	114	116	6.1	12.1	0.51	≤24	2.6	9.5	0.28
Ahlmark et al (12)	69*	93*	7.2	11.8	0.61	≤24	1.4	9.7	0.15
Multicentre International Study (28)	1533	1520	6.7	8.4	0.80	≤1	2.9†	4.2†	0.70
Norwegian Multicenter Study (27)	945	939	10.4	16.2	0.64	≤24	7.0	11.7	0.60
BHAT (18)	1916	1921	7.2	9.8	0.74	≤1	3.3	4.6	0.72
Hansteen et al (23)	278	282	9.0	13.1	0.69	≤1	4.0	8.2	0.49
Julian et al (25)	873	583	7.3	8.9	0.82	≤24	5.5	6.5	0.84
Total	5728	5454	7.7	10.7	0.72		4.2	6.3	0.67

I, intervention patients; C, control patients; RR I:C, risk ratio, intervention: control; D, dose.

* Incomplete reporting.

† Sudden cardiac death rates underestimated because of missing information.

Adapted with permission from Frishman WH, Laifer LI, Furberg CD. β-Adrenergic blockers in the prevention of sudden death. In: Josephson ME, ed. Sudden cardiac death. Philadelphia: F. A. Davis, 1985:249–264.

are reduced by 20% in these trials, the sudden cardiac death rate is reduced to a greater extent.

In the five largest trials, the intervention:control risk ratio for nonsudden death ranged from 0.75 to 1.02 (18, 23, 25, 28). The two smallest trials had the most favorable risk ratios of intervention to control—that is, 0.51 and 0.61 for all-cause mortality, and 0.25 and 0.15 for sudden cardiac death (12, 31). However, these same studies had intervention-to-control risk ratios of 1.4 and 2.8 for nonsudden death. Moreover, it may be argued that this unfavorable difference in nonsudden cardiac death may relate to the specific β-blocker used; however, a more probable explanation is the potential for chance associated with small patient numbers.

For witnessed instantaneous deaths, an even larger relative benefit from β-blocker therapy was recorded. The reduction was 59% in one study (27), 46% in the second (23), and 37% in the third (17), corresponding to an average reduction in instantaneous death of 46%. For these three trials, the pooled reduction in all-cause mortality was 31%, indicating that the relative reduction in instantaneous deaths is about 50% higher than that in all-cause mortality. When the instantaneous deaths are removed from the all-cause mortality, the pooled reduction in death in the remaining patients becomes 23%, and the relative reduction in instantaneous deaths is twice as great.

Three of the seven trials included 24-hour ambulatory electrocardiographic (ECG) records on a subset of participants, both at trial entry and at a subsequent follow-up visit (18, 25, 27). The findings of these three trials are similar. In the subgroup of survivors who entered the trial with frequent ventricular premature beats, fewer patients demonstrated this type of arrhythmia at a later follow-up visit than in the placebo groups (25, 32, 33). Among patients with frequent ventricular premature beats at entry, many continued to have this type of arrhythmia at followup, although fewer patients on β-blockers than on placebo did (25, 32, 33). Even though the recorded episodes of ventricular tachycardia were few in all trials at follow up, this arrhythmia was less common in patients receiving β-blockers than on placebo.

In the trials, a higher serum potassium and a shorter corrected ECG QT interval were noted in patients receiving β-blockers compared with those receiving placebo (22, 25, 34). β-Blockers have been observed to attenuate transmembrane potassium fluxes in response to high catecholamine levels (35). Perhaps part of the protective effect of β-blockade comes from its ability to preserve normal serum potassium levels, especially in those patients receiving concurrent diuretic therapy (34).

Anti-Ischemic Effects. Given that the incidence of nonsudden cardiac deaths and nonfatal reinfarction were reduced by β-blockade in the long-term trials, the anti-ischemic actions of the drugs also may have contributed to their beneficial effects in the period following the myocardial infarction.

Stimulation of cardiac β-adrenergic receptors by endogenous catecholamines increases myocardial oxygen consumption, and can thereby aggravate the ischemic process. Drugs that block the β-adrenergic receptor reduce the effects of catecholamines and decrease myocardial oxygen requirements by reducing systemic arterial pressure, heart rate, and myocardial contractility at rest and during exercise (5, 8). The effects of these drugs on coronary blood flow are less well defined. β-Blockers may decrease coronary blood flow by allowing the unopposed influence of coronary vasoconstrictor impulses to prevail. Furthermore, these drugs may also augment or maintain overall coronary blood flow by slowing the heart rate and increasing diastolic perfusion time (5, 8, 36). More controversial are those studies reporting favorable effects of β-blockers on myocardial metabolism, the coronary microvasculature, collateral blood flow, the distribution of myocardial blood flow, and oxygen-hemoglobin affinity. One or several of these anti-ischemic mechanisms may underlie the beneficial effects of β-blocker therapy in survivors of myocardial infarction.

Prevention of Atherosclerotic Plaque Tears. Coronary thrombi large enough to be detected by angiography are often associated with tears (fissures) in the caps of atherosclerotic plaques (37, 38). These tears allow blood to penetrate into the arterial wall, leading to thrombus formation within the intima; this may be followed by propagation of thrombosis into the vessel lumen. This process was described over 60 years ago (39, 41); however, its clinical importance has been realized more recently, after the microanatomy of coronary thrombi was established by serial histological sectioning (42–45). Plaque tears have been recognized in the angiograms of living patients with unstable angina (46, 47) and acute MI (48, 49), and in patients resuscitated from sudden cardiac death (50). Angioscopy in living patients with unstable angina has also confirmed the presence of mural thrombi on torn atherosclerotic plaques in the coronary arteries (51, 52).

Why a plaque becomes susceptible to rupture is not known. It is presumed to be a dynamic, reversible disorder caused by changes in the constituents in the plaque, its blood supply through the vasa vasorum, or the functional integrity of the overlying endothelium (53). Computer modeling of different forms of plaque have shown that the distribution of circumferential tensile stress across the intima can be radically influenced by atherosclerotic plaques. Regions of high circumferential stress correlated closely with the sites of intimal tears found on autopsy.

It has been proposed that sudden increases in blood pressure precipitated by physical or mental stress and surges in sympathetic tone could produce hemodynamic changes leading to plaque rupture. These surges in sympathetic nervous activity could also increase platelet aggregability and possibly coronary vascular tone. β-Adrenergic blockade may modulate or attenuate the consequences of these sympathetic nervous system surges by inhibiting the effects of catecholamines on blood pressure, heart rate, and myocardial contractility (54).

β-Blockers are known to protect the aorta from acute dissection, as well as reducing the incidence of recurrent dissection (8). This is accomplished, in part, by the ability of β-blockers to reduce blood pressure and myocardial contractility. Comparing propranolol with hydralazine, using Doppler ultrasonography, Spence found that propranolol was more likely to reduce the velocity of blood flow and the likelihood of nonlaminar blood flow in the aorta (55), thereby reducing turbulence and vortex formation (as heart-rate blood-velocity product is a determinant of arterial blood-flow disturbance). It is postulated that this effect of β-blockers could also reduce the risk of endothelial damage and plaque rupture; subsequent coronary thrombosis would be less likely to occur. In addition, some β-blockers also have weak anti-platelet effects which, in addition, might prevent the development and propagation of clots (7, 56).

Beta-Adrenoceptor Blockade in the Early Phase of Infarction

β-Adrenergic blockers have been considered for use as standard therapy in patients with acute MI in order to prevent the undesirable consequences of increased sympathoadrenal discharge, arrhythmogenesis, and extension of myocardial injury (9, 18, 57). The drugs can alter those factors that determine increases in myocardial oxygen consumption, and may augment coronary blood flow by increasing diastolic perfusion time (36). The β-adrenergic blockers also may reduce the incidence of occurrence of ventricular fibrillation.

On the other hand, β-adrenergic blockade can have unfavorable consequences in some cases of acute infarction. Cardiac impulse formation may be impaired greatly and conduction diminished to a degree that causes cardiac arrest (36). Furthermore, exacerbation of congestive heart failure in those patients dependent on the positive inotropic effect of catecholamines is a well-recognized sequela of the administration of β-adrenergic blockers.

Clinical Trials. Intravenous (IV) administration of a β-blocker within a few hours after the onset of chest pain markedly reduces pain and the need for narcotic analgesia in patients with MI (58). Pain relief is associated closely with a reduction in the systolic blood pressure and heart-rate product. β-Blockade also reduces the number of episodes of ventricular fibrillation compared with placebo treatment in patients with MI (58). Using crude measures of infarct size, such as cumulative creatine phosphokinase (CPK) release and development of Q waves on the ECG, it is clear that β-blockade is associated with less CPK release and better preservation of the R wave on the ECG than placebo (9, 10, 58–67). β_1-adrenergic blockade appears to be necessary. Compared with placebo, β-blockade diminishes the pyrexial response that accompanies MI (58), preserves serum potassium at a more normal level (34, 68), and often reduces the number of patients with threatened infarction going on to frank infarction (58, 67).

It has been suggested that β-blocker treatment should begin when the patient is admitted to the hospital to reduce the high rate of mortality among in-patients. In general, short-term intravenous treatment trials were designed to provide information about infarct size, arrhythmias, and pain relief, not mortality (9, 10, 58). In three large studies in which intravenous β-blocker treatment was followed by oral treatment, a true reduction of about 15% was observed in the in-patient mortality compared with placebo or control (9, 57, 69).

The Metoprolol in Acute Myocardial Infarction (MIAMI) study set out to evaluate the effect of metoprolol on mortality in patients entering the hospital within 24 hours of the onset of chest pain (70). Included in the study were 5,778 patients considered to be in a low-risk category, in that patients with bradycardia, hypotension, and left ventricular failure were excluded. Patients received either placebo or intravenous metoprolol (15 mg) followed by oral metoprolol for 15 days. A nonsignificant reduction in mortality of 13% was observed (70). Retrospective subgroup analysis suggested that an older population of patients with associated risks (previous angina, previous infarction, diabetes) experienced a 29% reduction in mortality (70).

The First International Study of Infarct Survival (ISIS-I) was a large, simple, open, randomized investigation designed to establish the effect of short-term atenolol treatment on total mortality and cardiovascular mortality at one week and one year after the onset of chest pain (57). Intravenous atenolol (5–10 mg) was administered, followed by oral atenolol, 100 mg daily for one week. As in the MIAMI trial, a low-risk population was studied (4.5% mortality at one week in the control group) (57). Over 16,000 patients were randomized; 80% were admitted to the study within eight hours of chest pain. A significant reduction in cardiovascular mortality of 15% was observed with atenolol therapy. The benefit of atenolol was confined to the first 36 hours. The reduction in mortality on day 0 to day one was 32% (similar to that observed in the MIAMI study). Nonfatal cardiac arrests were not reduced by atenolol treatment, suggesting a reduction in infarct size as a cause for the mortality reduction (57, 58).

Patients in ISIS were followed up for one year. The cardiovascular mortality was 10.1% in the atenolol group and 11.3% in the control group, representing a 10.6% reduction in mortality (57). The extra lives saved during days 8 to 365 were most likely related to intravenous β-blockade because, at hospital discharge, more patients in the atenolol group remained on β-blocker than in the control group (35% vs 26%) (57). An early intervention study in 1,395 MI patients randomized to receive metoprolol intravenously, followed by 200 mg per day orally or placebo for three months (69), showed that the significant early benefit in mortality reduction at 90 days was still present two years later. The benefit, however, was not present five years later (71).

Clinical Use

It has been demonstrated conclusively that β-blockers can prolong life in patients who have had infarction (10).

Selection of Patients. Should all patients receive β-blockers after an MI? There are obvious contraindications to the use of β-blockers, such as advanced congestive heart failure, Raynaud's phenomenon, bronchospastic conditions, significant disorders of atrioventricular and sinus node function, and possibly vasospastic angina. These conditions restrict the postinfarction population in whom β-blocker therapy can be administered. Moreover, in the major postinfarction β-blocker studies, approximately 50% of the eligible patients (including many high-risk individuals) were excluded (10). Similar selection of patients should be utilized if comparable mortality reduction is to be achieved in standard clinical practice.

It appears from the findings of recent studies that the greatest benefit from β-blocker therapy is achieved in patients who are over 60 years of age, and in the medium- or high-risk postinfarction groups (patients with LV dysfunction or arrhythmias (9, 10, 72). There is serious question whether low-risk postinfarction patients (first infarct, no LV dysfunction, normal predischarge exercise test results, and absence of complex ventricular arrhythmias), whose mortality one year after hospital discharge is 2%, require prophylactic treatment with β-blockers (72). It also is not known whether β-blockers should be used as long-term prophylactic therapy in those patients who have undergone successful coronary bypass surgery or angioplasty (10). Postinfarction patients who develop angina pectoris, hypertension, supraventricular arrhythmias, or strongly positive graded exercise tests should be considered for treatment with β-blockers as soon as these indications arise (10).

Choice of Agent and Treatment Design. Is one β-adrenergic blocker superior to another in survivors of acute MI, or is there a common protective effect seen with all the drugs in this class? Trials investigating eight different β-blockers found favorable mortality trends, suggesting that the benefit is conferred by the drug class rather than by a specific β-blocker.

When should treatment be initiated with β-blockers, by what route, at which dose, and for how long? It appears from multiple studies that β-adrenergic blockade can be initiated early and safely to hemodynamically stable patients with and without thrombolysis (approximately 50% of patients with MI) (9). Caution should be taken in administering β-blockers to patients with transmural inferior wall MI, where hemodynamic complications of a right ventricular infarction might be unmasked.

- Timolol was the first orally active β-blocker to be approved by the FDA as a long-term prophylactic agent in survivors of an acute MI at a fixed daily dose of 20 mg in two divided doses.
- Propranolol was also approved for this use at a range of 180–240 mg daily in two to three divided doses, to begin 5 to 21 days after the onset of infarction.
- Intravenous metoprolol and atenolol are currently approved for use in MI. Oral metoprolol in doses of 100 mg twice daily and oral atenolol are approved for long-term use.

Whether the sustained-release form of propranolol or metoprolol will be effective as a postinfarction treatment needs to be determined. It also is not clear whether a fixed-dose regimen of these drugs is preferable to a titration until clinical β-adrenergic blockade is achieved.

Safety Profiles. Is there a difference in the postinfarction safety profiles of the different β-blockers? Severe side effects from β-adrenergic blocking drugs were infrequent in the postinfarction trials. Compared with placebo, there appeared to be a higher incidence of symptomatic congestive heart failure, sinus bradycardia, hypotension, bronchial obstruction, fatigue, and mental depression with the β-blockers (73, 74). Caution still should be exercised, however, when using β-blockers in high-risk patients whose myocardial function may be dependent on stimulation from the sympathetic nervous system. The different β-blockers used in these trials appeared to demonstrate comparable safety profiles, except for practolol, which caused a unique series of side effects, leading to its withdrawal from the world market (10).

No conclusive data are available regarding the effect of β-blocker therapy on mortality if the drugs are started months to years after acute infarction. Nevertheless, it is reasonable to assume that mortality and morbidity would be reduced if treatment were initiated within a few months after hospitalization. Support of this view arose from retrospective subgroup analyses of a long-term prevention study with oxprenolol in coronary heart disease. A beneficial effect on survival was noted if treatment began within four months of an acute MI but no benefit if therapy began four months or more after the event (29).

Some studies suggest that the major beneficial effects of β-blockers accrue during the first 12–18 months following infarction, and that the incremental benefit thereafter is small (75). Limited information from one trial shows more deaths in the placebo treatment group than in the β-blocker group for a period as long as 72 months (75), which suggests a sustained benefit from continued therapy.

If one is concerned with the extended use of these drugs in the general postinfarction population, patients in the intermediate and high-risk subsets, who benefit the most from β-blocker therapy, might be candidates for longer courses of therapy. An argument for stopping β-blocker treatment after a fixed time period stems from the recent observation that some β-blockers can lower plasma high-density lipoprotein cholesterol levels and triglyceride levels, potentially increasing the risk of atherogenesis (76). Whether this should be a concern in patients who already have advanced heart disease is debatable.

Finally, results of the long-term postinfarction trials yielded no evidence of a β-blocker "withdrawal reaction" in patients who discontinued active treatment (77). Patients who require continued β-blocker treatment for other reasons (angina pectoris, hypertension, migraine, and arrhythmias) should be maintained on this treatment regimen as needed.

Beta-Blocker Therapy and Coronary Reconstruction. How will postinfarction β-blocker therapy affect utilization of coronary reconstructive procedures in this population? Myocardial revascularization surgery appears to be of benefit in patients with significant angina and angiographically documented severe left-main or three-vessel coronary artery disease. Therapy with β-blockers should reduce the frequency and severity of angina and, therefore, may diminish clinical indications for coronary angiography and bypass surgery. In addition, because β-blockers confer a documented reduction in one-year postinfarction mortality, risk-benefit considerations may now favor continued medical therapy, rather than surgical intervention, in many patients (10, 72).

Mechanism of Protection. How do β-blockers protect certain patients with previous MI from reinfarction and death? By virtue of their basic pharmacologic actions, the drugs, as a group, can attenuate sympathetic cardiac stimulation and perhaps the potential for plaque rupture, coronary thrombosis, reentrant ventricular arrhythmia and sudden death (54). The drugs inhibit lipolysis and can reduce stress-induced increases in free fatty acids that can induce arrhythmia. All β-blockers have been found to exert a powerful suppressive effect on plasma renin levels (8). Owing to the concomitant aldosterone-lowering effect and inhibitory actions on transmembrane potassium fluxes, β-blockers may also protect patients from the dangers of hypokalemia (8, 35). The drugs may prevent formation of free radicals (78).

The platelet-inhibiting actions of some β-blockers probably do not contribute to their benefit in infarct survivors, given that this effect is related to nonspecific membrane stabilization and not to β-adrenergic blockade (timolol lacks this membrane-stabilizing property) (10). Other less probable mechanisms for benefit include favorable effects on the oxygen dissociation curve (10) and reduction in transmembrane myocardial calcium fluxes (10).

Conclusion

Independent of mechanism, appropriate use of β-blockers in postinfarction patients should improve the outcome of many patients with MI. The addition of β-blockers to acute thrombolysis may improve patient outcome to a greater extent than either drug alone. This was suggested by the results of the Thrombolysis in Myocardial Infarction (TIMI-II) study, in which metoprolol was combined with recombinant tissue plasminogen activator (rt-PA) in patients with MI (79). The benefit of combining β-blockers with antiplatelet agents and calcium-entry blockers to further improve long-term patient outcome also needs to be examined.

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A Simple Spirometric Clue to Asthma:

Airways Obstruction Suggested by Negative or Reduced Forced Expiratory Reserve Volume Despite Normal FEV_1-FVC Ratio

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Abstract

I report on 25 asthmatic patients in whom airways obstruction was not detectable by conventional spirometric indices, but was suggested by a reduced or negative forced expiratory reserve volume (FERV), that is, the ERV measured from the forced vital capacity (FVC) maneuver and preceding tidal breaths. Patients with known causes for reduced ERV were excluded. The ratio of forced expiratory volume–1 sec (FEV_1) to FVC was normal or high in all 25 patients, and the forced expiratory time $(FET)_{25-75\%}$ was normal in half (12). Using conventional spirometric algorithms, the condition of most (76%) of the patients would be interpreted as "restrictive impairment."

The FERV is easily measured in a physician's office or clinic. If this simple test is to provide a clue to the presence of airways obstruction that is otherwise not demonstrable spirometrically, the FVC maneuver must be maximal and reproducible and the preceding tidal breaths, as well as the FVC, must be graphically recorded.

THE EXPIRATORY reserve volume (ERV) is defined as the difference in volume between the resting expiratory level and maximum expiration achieved after a complete unforced (that is, slow) expiration. The ERV may also be calculated from a forced vital capacity (FVC) maneuver. I have called this measurement the "forced expiratory reserve volume" (FERV); it may also be called "effort-dependent ERV" to emphasize an effect from the forced (that is, rapid) expiration.

In reviewing spirometric data, including tracings of the FVC and antecedent tidal volumes, I have noted that an FERV that is markedly reduced, to less than 10% of the predicted vital capacity (VC), or even negative (that is, the spirographic tracing of the FVC does not return to baseline) has often been a useful clue to an underlying obstructive disorder not otherwise apparent from the spirometric results.

This finding, from a simple recording spirometer, was present in 25 asthmatic patients even when, secondary to air trapping or other mechanisms, the FEV_1-FVC ratio and flow rates (calculated relative to the FVC) were normal or increased and the forced expiratory time $(FET)_{25-75\%}$ was not prolonged. The latter measurement is useful because it is less altered than flow rates by a reduction in FVC.

Since a reduced or negative FERV can result from an incomplete expiratory effort, it was necessary to ensure that efforts were maximal, reproducible, and reached a plateau where volume did not change. Additionally, patients with known causes for reduced ERV, including obesity, were excluded.

The pattern of a reduced or negative FERV and normal or high FEV_1-FVC ratio and flow rates was observed in 25 patients of all ages with known asthma. The FVC was usually decreased. Since a decrease in the FEV_1-FVC ratio is considered the spirometric hallmark of airways obstruction, the presence of an underlying obstructive disorder would not have been detected in these patients (1, 2), and any reduction in FVC

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TABLE

Pulmonary Function in Illustrative Cases

	Pt. 1, 54-year-old man		Pt. 2, 40-year-old man	
	↓ FERV noted	2 years earlier	↓ FERV noted	5 months earlier
FERV (mL)	−150 to +250	—§	160–340	—
FVC (L) baseline	2.82 (72% pred‡)	3.44 (82% pred)	1.65 (33% pred)	2.80 (62% pred)
FVC BD* or Meth† (L)	3.27 BD (84% pred), ↑ 16%	2.84 Meth (68% pred), ↓ 17%	1.84 BD (41% pred), ↑ 12%	—
FEV$_1$ (L) baseline	2.25 (79% pred)	2.34 (77% pred)	1.20 (34% pred)	2.20 (62% pred)
FEV$_1$ BD or Meth (L)	2.56 BD (91% pred), ↑ 14%	1.78 Meth (59% pred), ↓ 24%	1.44 BD (42% pred), ↑ 18%	—
FEV$_1$-FVC baseline	0.80	0.68	0.74	0.79
FEV$_1$-FVC BD or Meth	0.78 BD	0.63 Meth	0.78 BD	—
FEF$_{25-75\%}$ (L/sec) baseline	2.7 (88% pred)	1.0 (29% pred)	1.0 (24% pred)	2.3 (59% pred)
FET$_{25-75\%}$ (sec) baseline	0.52	1.72	0.83	0.61
TGV (L) baseline	—	3.07	—	—
TLC (L) baseline	—	5.81 (90% pred)	—	—
RV (L) baseline	—	2.37 (104% pred)	—	—

* BD, postbronchodilator.

† Meth, postmethacholine.

‡ pred, % predicted.

§ —, not studied.

would have been attributed to a "restrictive impairment."

Methods

A total of 400 spirographic tracings made within a four-year interval (1981–1984) at the author's off-campus office were reviewed to identify the presence of a markedly reduced or negative FERV. Since the ERV is normally 20%–40% of the vital capacity (3), an FERV <10% of the predicted VC was considered markedly reduced. A negative FERV was present when the spirographic tracing of the FVC did not return to the baseline end-expiratory level. Patients with a low FEV$_1$-FVC ratio (see below), obesity (>125% of ideal body weight specified by the Metropolitan Life Insurance Company), cardiac failure, interstitial lung disease, neuromuscular or skeletal disorders, pregnancy, ascites, or bullae on chest radiograph were excluded. The 25 remaining patients were all diagnosed as having bronchial asthma. Their clinical and functional characteristics are described in the Results section.

The FVC was performed according to American Thoracic Society specifications (4) using a water-sealed spirometer (Godart Pulmonet) to record a volume-time curve (spirogram) and/or a rolling-seal spirometer (Gould) to record a maximum expiratory flow-volume (MEFV) curve. Efforts were reproducible and reached a plateau at which no further volume change was measured. The end-expiratory level of the FVC maneuver was compared to that of the preceding tidal breaths, the difference being the FERV. Maximum voluntary ventilation (MVV) was measured using the same instruments. A slow or inspiratory VC was not uniformly measured. Patients were tested standing and using noseclips. Predicted values were based on a recalculation of Miller et al for spirometry (5) and on Baldwin et al (6) for MVV. A normal value for FVC, FEV$_1$, and MVV was defined conventionally as ≥80% of predicted value; normal value for residual volume (RV) was defined as 80%–120% of predicted value. Lower limits of normal FEV$_1$-FVC ratios were 0.70 (up to age 60 years) and 0.65 (age ≥ 60 years) (7). The upper limit of normal for the FET$_{25-75\%}$ was 0.77 sec, equivalent to a ratio of forced expiratory flow (FEF)$_{25-75\%}$ to FVC of 0.65 (8, 9).

Of the 25 patients, 15 had spirometry repeated after a bronchodilator aerosol to assess bronchial reactivity; a positive response was defined as an increase in FEV$_1$ > 10% from baseline (8). Two of the remaining 10 patients had methacholine provocation at The Mount Sinai Hospital, New York City, using five inspiratory capacity breaths of graded concentrations delivered by a deVilbiss No. 46 nebulizer for 0.6 sec. Three of the 15 patients who had bronchodilator aerosol later underwent methacholine provocation at the same laboratory. All 5 who underwent provoca-

TABLE *continued*

		Pt. 19, 64-year-old woman	
	Pt. 3, 59-year-old woman	↓ FERV noted	6 weeks later
FERV (mL)	−150	150–200	—
FVC (L) baseline	1.52 (56% pred)	1.85 (75% pred)	2.12 (88% pred)
FVC (L) BD or Meth (L)	1.65 BD (61% pred), ↑ 9%	—	1.58 Meth (66% pred), ↓ 25%
FEV_1 (L) baseline	1.20 (60% pred)	1.48 (85% pred)	1.62 (94% pred)
FEV_1 BD or Meth (L)	1.36 BD (68% pred), ↑ 13%	—	1.18 Meth (69% pred), ↓ 27%
FEV_1-FVC baseline	0.82	0.80	0.76
FEV_1-FVC BD or Meth	0.82 BD	—	0.75 Meth
$FEF_{25-75\%}$ (L/sec) baseline	1.1 (40% pred)	1.52 (65% pred)	1.46 (63% pred)
$FET_{25-75\%}$ (sec) baseline	0.69	0.61	0.73
TGV (L) baseline	1.90	—	2.77
TLC (L) baseline	3.60 (89% pred)	—	4.55 (105% pred)
RV (L) baseline	1.78 (136% pred)	—	2.30 (120% pred)

tion showed a decrease in $FEV_1 > 20\%$ at concentrations $\leqslant 2.5$ mg/ml. Six patients had full lung volumes measured by body plethysmography (Gould) at this laboratory, where predicted values for total lung capacity (TLC) and residual volume (RV) were derived from the RV-TLC ratios of Goldman and Becklake (10) and the VC values of Miller et al (5). The hospital tests were usually performed at a time different from that of the reported FERV.

Results

All 25 subjects were off-campus outpatients seen by a single pulmonologist over a four-year span. Of the 25, 21 were clinically diagnosed as having bronchial asthma based on evidence of airways obstruction that reversed either spontaneously or with therapy; several were taking bronchodilator medications. Many had been hospitalized in the preceding two years for bronchospasm; 2 of these were woodworkers who had noted exacerbation of their asthma when working with certain woods or wood laminates. Five of the 21 had coexisting chronic bronchitis, classified as "asthmatic bronchitis." The remaining 4 patients had hyperreactive airways demonstrated by methacholine provocation. As stated, all patients had a normal FEV_1-FVC ratio. There were 13 men and 12 women, ranging in age from 33 to 83 years (mean 56.9 years); 12 patients were lifetime nonsmokers. Chest radiographs were normal or showed evidence of hyperinflation.

Pulmonary function findings in 4 illustrative cases are shown in the Table. In 12 patients, the FVC and FEV_1 were proportionately reduced (values within 5% of predicted of each other; in 2

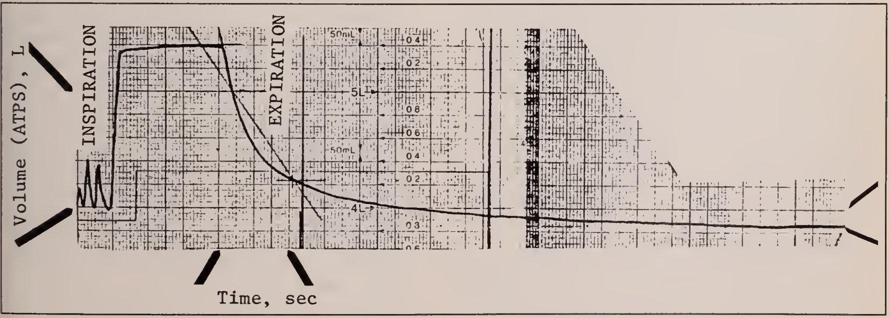

Fig. 1. Patient no. 9, an 83-year-old woman: spirogram showing resting tidal breaths and FVC maneuver; FVC (1.67 liters, 85% of predicted), FEV_1 (1.27 L, 100% of predicted), and configuration are normal; FERV (delineated by arrows at right side of print) is 150 ml at ambient temperature and barometric pressure, saturated with water vapor (ATPS). Scale: one liter (ATPS) is indicated by arrows at left, on y axis, one intermediate box = 200 mL on that axis; 1 sec is indicated by arrows at bottom, on x axis, one intermediate box = 0.25 sec on that axis.

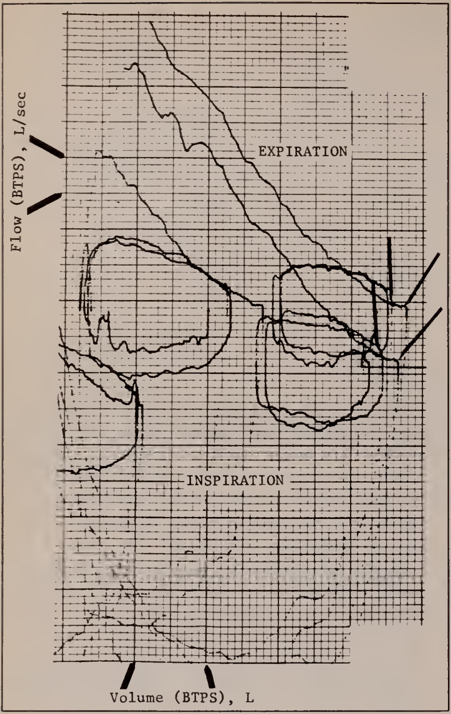

Fig. 2. Patient no. 4: three sets of maximum expiratory (above-baseline) and inspiratory (below-baseline) flow-volume curves, each showing one or more resting tidal breaths and the FVC maneuver; configurations of the maximal expiratory and inspiratory loops are normal; FERV, calculated from the rightmost two curves and delineated by light arrows, was approximately 250 and 300 mL at body temperature and barometric pressure, saturated with water vapor (BTPS). Scale: one liter per second (BTPS) is indicated on y axis by arrows, one small box = 200 mL/sec on that axis; 1 L is indicated on x axis by arrows, one small box = 100 mL on that axis.

patients in this group, the FVC was just above and the FEV_1 just below normal). The forced expiratory time over the middle half of the FVC ($FET_{25-75\%}$), also called the midexpiratory time (MET), another measurement of airways obstruction, was abnormal (>0.77 sec) in 10 of these 12 patients (mean 1.02 sec, range 0.69–1.67).

In 9 patients, the FVC was reduced disproportionately to the FEV_1. In 5, both the FVC and FEV_1 were abnormal (for example, patient no. 1), and in 4, only the FVC was abnormal (for example, patient no. 19). The FEV_1-FVC ratio was *increased* (>0.85) in 6 of the 9 patients in this group. The $FET_{25-75\%}$ was *not prolonged* in any of these patients (mean 0.46 sec, range 0.26–0.67); 7 of the 9 had values below 0.54 sec.

In 4 patients, the FVC and FEV_1 were both normal. In 3 of these patients, the FVC was smaller than the FEV_1 by an amount equivalent to 5% or more of the predicted value. The $FET_{25-75\%}$ was slightly increased in 3 of the 4 patients (mean 0.79 sec, range 0.67–0.86).

The configurations of the spirographic and MEFV curves were generally normal (Figs. 1, 2) or restrictive (Fig. 3). On the flow-volume recordings, flows during tidal breathing often exceeded those on the MEFV curve (Figs. 2, 3).

Two brief case descriptions are typical:

Patient No. 1, a 52-year-old black, male, nonsmoking woodworker, had had no respiratory problems until he began working with urea formaldehyde cements six months earlier, at which time he noted chest heaviness, exertional dyspnea (one to two flights), and occasional wheezing. When first seen on July 12, 1980, his lungs were clear. The FVC was 3.32 L (80% of predicted), FEV_1 2.60 L (86%), FEV_1-FVC ratio 0.78, and $FET_{25-75\%}$ 0.72 sec; bronchodilator response was negative. One month later (Table), the FEV_1 was 260 ml smaller, the FEV_1-FVC ratio was slightly decreased, and the $FET_{25-75\%}$ was clearly prolonged; methacholine provocation was positive at a concentration of 0.62 mg/ml. The symptoms were moderately controlled by bronchodilator medications and inhaled beclomethasone but flared on exposure to smoke or strong odors. The

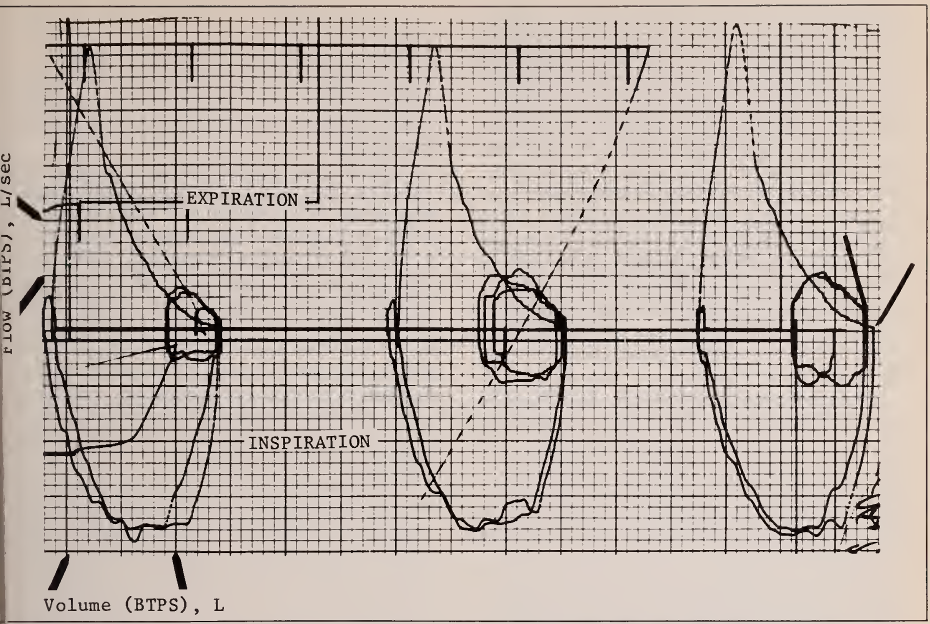

Fig. 3. Patient no. 3: three sets of maximum flow-volume curves measured on different day than results shown in Table 1: FVC (1.63 L), and FEV_1 (1.31 L) are both reduced, similar to results in Table. Configurations of expiratory curves are restrictive, and of inspiratory curves, normal; FERV ranged from 0 to 80 mL BTPS, the latter delineated by light arrows at right side of print. Heavy line is flow baseline. Scale as in Fig. 2.

restrictive spirometric values and reduced FERV in the first column of the Table were obtained on June 26, 1982, when examination revealed diminished breath sounds and slight wheezing.

Patient No. 2, a 40-year-old white, male nonsmoker, with a history of asthma as a child, sought medical attention on June 11, 1984, for nocturnal wheezing. Minimal wheezes were auscultated. Spirometric values were "restrictive" (Table, second column). When next seen (on Nov. 5, 1984), he was short of breath and wheezing more than previously (both symptomatically and on examination). He now showed a markedly reduced FERV and a marked decrease in FVC (decreased 1.15 L), and FEV_1 (decreased 1.0 L) from values five months earlier, with a normal FEV_1-FVC ratio, minimally prolonged $FET_{25-75\%}$, and positive bronchodilator response. He has since done well on bronchodilator medications and inhaled beclomethasone but requires occasional systemic corticosteroids.

Of the 15 patients who received a bronchodilator aerosol at the time the FERV was recorded, 9 had positive results.

Methacholine provocation in 5 patients was positive at low concentration. When the baseline FEV_1-FVC ratio was normal, falls in FVC and FEV_1 were similar (for example, patient no. 19), so that the postmethacholine FEV_1-FVC ratio and flow rates (measured in relation to the smaller FVC) did not appear to be abnormal.

Of the 6 patients whose RV was measured, values were normal in 3 and increased (136%–192% of predicted) in 3; TLC was increased in 1 patient (131% of predicted). As stated above, these studies were usually performed at a time different from the FERV reported, when the patients' clinical status and pulmonary function had often changed.

Since the initial observations of a reduced FERV and normal FEV_1-FVC ratio, 7 of the 25 patients have been tested on revisits and had a similar constellation of findings.

Discussion

The definition of a "reduced" FERV in this paper is arbitrary; a value less than 10% of the predicted FVC was chosen, since the ERV in normal subjects ranges from 20% to 40% of the FVC (3). A reduced or negative FERV can result from a number of clinical conditions (for example, airways obstruction manifested by a reduced FEV_1-FVC ratio, chest bellows disorders, obesity); patients with such conditions were excluded from the series reported in this paper. A common artifact producing this finding is early cessation of expiration during the FVC maneuver, which would also decrease the FVC and increase the FEV_1-FVC ratio and flows. This was excluded by careful monitoring of subject effort and adherence to American Thoracic Society standards for performance of spirometry (4); expiratory efforts were maintained until change in volume was not discerned on the tracing.

It is recognized that patients tested in a clinical facility may not demonstrate a consistent end-expiratory level during tidal breathing from which to calculate the FERV. It is nevertheless general practice to ascertain this level (which denotes the functional residual capacity) and use the ERV measured relative to this for calculating various lung volumes.

After elimination of those with disorders known to be associated with reduced ERV, all 25 patients uncovered by review of spirometric tracings could be diagnosed as having asthma: 21 were diagnosed on clinical grounds and 4 on the basis of positive methacholine provocation. Airways obstruction was not apparent from the spirometry performed at the time the reduced FERV was observed, in that all patients had normal FEV_1-FVC ratios. Indeed, 19 of the 25 patients (76%) would be reported by several spirometry interpretation algorithms (1, 2) to have "restrictive impairment," since only the FVC was reduced (4 patients), both the FVC and FEV_1 were reduced but the FVC was disproportionately reduced (5 patients), or both the FVC and FEV_1 were proportionately reduced (10 patients). Four additional patients had normal values for FVC and FEV_1 as well as for the FEV_1-FVC ratio, which would be reported as "normal spirometry."

The findings in these patients are presented because they may be suggestive of an underlying obstructive disorder that would otherwise not be apparent. The prevalence of this constellation (a reduced or negative FERV in the presence of a normal FEV_1-FVC ratio) in the overall asthmatic population cannot be inferred, since it would depend on the makeup of the population, the severity of illness, and the indications for spirometry at a particular facility. It is well known that asthmatics in remission frequently have normal spirometry or reduced flows at low lung volume with a normal FEV_1-FVC ratio.

The apparent absence of airways obstruction using the FEV_1-FVC ratio was supported by the configurations of the spirographic or MEFV curves which were normal (Figs. 1, 2) or restrictive (Fig. 3).

Greater flows on tidal rather than maximal expiration, seen in several of the MEFV curves (Figs. 2, 3), are another clue to obstruction akin to partial expiratory flow volume curves (11). Other measurements of obstruction were often misleading, as illustrated by the $FET_{25-75\%}$. This measurement is cited because it is useful for detecting airflow limitation when the FVC is reduced, since flow rates are often decreased when the vital capacity is decreased. The $FET_{25-75\%}$ is relatively independent of changes in lung volume and correlates strongly with specific airway conductance (12, 13). The $FET_{25-75\%}$ was *not* prolonged in half the patients.

The demonstration of a markedly reduced or negative FERV provided a simple spirometric clue to the presence of an underlying obstructive disorder in the 25 patients reported in this paper. This observation can be made only when a graphic record is made both of the FVC breath and of the tidal breaths that precede it. This finding is well known in patients with obvious obstruction (reduced FEV_1-FVC ratio, reduced flow rates, prolonged $FET_{25-75\%}$) but has not been described in the absence of these spirographic abnormalities.

A bronchodilator aerosol was administered to 15 patients because of the clinical likelihood of asthma and demonstrated hyperreactivity in 9. In clinical practice, a bronchodilator may not have been administered in the absence of obstruction.

Possible Mechanisms. The spirometric findings in these patients may be summarized as follows: a markedly reduced or negative FERV and a reduction in FVC equivalent to or greater than the reduction in FEV_1.

Several mechanisms may account for these findings. Air trapping due to diffuse narrowing of the airways is one. When patients are tested in a physician's office, full lung volumes are seldom available to demonstrate air trapping. When lung volumes are then measured at a laboratory, the clinical status is often different. In 3 of 6 patients in whom the measurements were made, the RV demonstrated hyperinflation (>135% of predicted), and in 3, the RV was normal. A slow or inspiratory VC maneuver may have provided suggestive evidence of air trapping if it greatly exceeded the FVC. Unfortunately, it was not uniformly performed.

Another possible mechanism for the findings is closure of airways rather than narrowing. The greater reduction in FVC than in FEV_1 in 12 of our 25 patients is similar to the baseline findings in "volume responders" to bronchodilators described by several investigators (14–16). Volume responders (those whose VC increases more than their FEV_1 after bronchodilatation) have greater baseline air trapping (mean VC 74% of predicted vs. 87% in "flow responders," mean RV 207% of predicted vs. 119%) (14) and show a postbronchodilation helium MEFV curve characteristic of small airways obstruction (15). The explanation proposed for the volume response was that the bronchodilator aerosol opens peripheral airways that were virtually closed. These closed airways would therefore not manifest themselves in an obstructive configuration to the spirographic or MEFV curve, and indeed might cause a restrictive contour if they result in a reduced FVC. The airways "recruited" by the bronchodilator are still constricted, and their relative contribution to total airway resistance is now greater (15).

Closure of the airways has also been described in young patients with seemingly mild bronchospasm. Obstruction is not detected presumably because flow is preserved in the remaining airways (17). Colp and Williams (18) described reversible occlusion of a main bronchus in one patient and presumed occlusions in the small airways in another patient with diffuse airways inflammation. They pointed out the misleading impression of restrictive impairment obtained from the decreased VC and normal FEV_1-FVC ratio and emphasized that recurrent, rapid, marked changes in FVC are not characteristic of restrictive impairment in interstitial lung disease. These authors reported that the FEV_1-FVC ratio was greater (and the FVC therefore smaller) in severe asthmatics than in patients with chronic obstructive pulmonary disease having similar values for FEV_1 and concluded that a preserved ratio in severe asthma suggests airways closure resulting from mucus plugging.

Diffuse closure of the airways may not result in air trapping. Hudgel and co-workers (19) reported a case of spasmodic occlusion of alveolar ducts and small airways, a condition they termed "reversible restrictive lung disease simulating asthma." This young woman manifested spontaneous as well as exercise-induced dyspnea without wheezing. During a typical episode, all lung volumes decreased markedly (TLC from 5.3 to 2.6 L, VC from 3.8 to 1.2 L), the FEV_1 fell from 3.0 to 1.0 L but the FEV_1-FVC ratio increased from 0.78 to 0.85, and specific airway conductance and flow rates measured at absolute lung volume increased. Static compliance decreased and elastic recoil increased. The authors attributed the changes to muscular constriction of alveolar ducts and small airways.

Summary and Conclusions

In summary, the mechanisms suggested may result in increased (air trapping) or decreased (closure of the airways at various levels) RV and TLC. Gilbert and Auchincloss (20) reported that 10% of patients with "pure obstructive defects by clinical and plethysmographic criteria showed a restrictive defect on the spirogram"; their definition of a restrictive defect is similar to that given in this paper, namely, a reduced FVC and an FEV_1-FVC ratio ≥ 0.70. Their patients, by definition, had hyperinflation.

The unavailability of full lung volumes and mechanics when the present observations were made precludes judgment on the mechanisms responsible for the patients' failure to exhibit spirometric findings characteristic of airways obstruction. Nevertheless, the patients demonstrate that the observation of a markedly reduced or negative FERV should alert the physician to the presence of an underlying obstructive disorder. This observation can be made in a physician's office with a simple recording spirometer.

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Regional Procurement and Export of Hepatic Allografts for Transplantation

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Abstract

A team dedicated to hepatic procurement exclusively for export to distant centers was established at The Mount Sinai Hospital in New York. Between January 1987 and March 1988, 20 livers were retrieved and sent to five institutions in the U.S. and Canada for implantation. These procedures were carried out in concert with local cardiac and renal procurement teams; 12 hearts and 34 kidneys were used from these 20 donors. Functional results of both the livers and the other organs were in line with nationally reported standards. The multi-organ procurement procedure was streamlined as a result of the coordination which developed between the teams. Savings in time and travel expense by skilled personnel were realized; in five cases no alternative hepatic procurement team was available. With the ability to preserve livers for increasingly long periods, this type of program will assume greater importance in the future.

THE procurement of extra-renal vital organs for transplantation, including the heart, heart-lung, and liver, has customarily remained the province and responsibility of the surgical team that will subsequently perform the transplant surgery. This is in distinct contrast to most renal procurement programs, where import and export is common. This is primarily due, in the case of the liver, to the technical complexity of the donor surgery and to the need for immediate organ function, which is dependent on optimal harvest procedures (1). This report describes our initial 13-month experience in the New York metropolitan area in hepatic procurement performed exclusively for export to distant centers for transplantation.

Materials and Methods

Between January 1987 and March 1988, 54 donors in the New York area were identified as medically suitable and consent was obtained for liver donation. A recipient institution with an appropriate candidate and an available recipient surgical team was identified in 37 of these cases. For the remaining 17 livers, suitable recipients could not be found and the organs were therefore not utilized. Once the recipient institution had accepted the donor liver, the services of the Mount Sinai Hospital liver procurement team were volunteered. In 20 instances, involving five recipient institutions in the United States and Canada, these services were accepted. In the remainder, the recipient center coordinated and carried out the organ retrieval.

From these 20 liver donors, a total of 34 kidneys as well as 12 hearts were harvested. Three infants between three and eight months of age were deemed unsuitable as renal or cardiac donors. The decision not to use three of the five remaining hearts was made preoperatively. In two other cases, the heart was rejected after open-chest evaluation by the cardiac team.

Eighteen harvest procedures were done using the rapid-flush technique (2, 3), which avoids extensive hilar dissection prior to perfu-

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sion; a formal hilar dissection was performed in the remaining two cases for teaching purposes. Following removal, the livers were further perfused with preservation solution (University of Wisconsin solution), enclosed in three sterile plastic bags, and placed on ice in an insulated crate for shipping.

The hospital chart of the donor and/or the transplant coordinator's notes were reviewed and the following information gathered: date of admission, age, sex, race, height, weight, cause of death, date placed on ventilator, blood group, number of transfusions, vasoactive medications and diuretics administered, blood pressure, electrocardiogram, chest x-ray and echocardiogram readings, liver enzymes, coagulation profile, BUN, and creatinine.

Approximately one week after transplant, the recipient surgeon or transplant coordinator was interviewed. Regarding the livers, the surgeons' assessments of immediate organ function and peak SGPT, SGOT, and total bilirubin levels were recorded. In the presence of a technically sound recipient procedure, the diagnosis of primary nonfunction was made if the patient required retransplantation within the first postoperative week. With regard to the kidney recipients, results were classified as primary function, delayed function (the need for dialysis in the first postoperative week), and primary nonfunction. In the heart recipients, ischemic time and patient survival data were obtained.

Results

The results presented here apply only to those donor operations performed by the Mount Sinai team; outcomes of organs retrieved by other groups were not investigated.

Donor age ranged from 3 months to 48 years (mean 22.2 years). Three infants were 3, 6, and 8 months of age. Ten donors were male. Fourteen were white, three black, two Hispanic, and one Oriental. Twelve patients were blood group O, five group A, two group AB, and one group B.

In seven cases, the cause of death was anoxia. Nine donors suffered head trauma due to motor vehicle accident, gunshot wound, or fall. The remaining four, all female, died of subarachnoid hemorrhage.

The mean duration of assisted ventilation prior to organ harvest was 4.5 days (range 2–17 days). Twelve patients required dopamine to maintain hemodynamic stability. Eight donors received at least one dose of vasopressin for diabetes insipidus. The systolic pressures varied from a mean low of 87.7 ± 16.6 mm Hg to a mean high of 118.5 ± 13.4 mm Hg. Donor laboratory parameters are summarized in Table 1.

TABLE 1
Laboratory Data, 20 Organ Donors, The Mount Sinai Hospital Procurement Team

Test	Peak value ± SD
SGOT	110 U ± 99 U
SGPT	76 U ± 93 U
Bilirubin	
total	1.0 mg% ± 0.8 mg%
direct	0.3 mg% ± 0.4 mg%
BUN	19 mg% ± 10 mg%
Creatinine	1.0 mg% ± 0.5 mg%

TABLE 2
Laboratory Data, 20 Liver Recipients, Organs Procured by The Mount Sinai Hospital Team

Test	Peak value ± SD
SGOT	
overall	2039 U ± 3712 U
primary function	956 U ± 758 U
SGPT	
overall	1006 U ± 1040 U
primary function	823 U ± 741 U
Total bilirubin	
overall	15.0 mg% ± 9.9 mg%
primary function	14.3 mg% ± 9.5 mg%

Livers. Four of the livers were found to have variations in arterial anatomy. Three of these received a left hepatic branch from the left gastric artery, and one received a right branch from the superior mesenteric artery. All organs were harvested regardless of arterial variations. There were no incidental injuries to the harvested organs in the course of procurement.

The method of harvest (rapid-flush vs. formal dissection) did not affect the results. All 20 livers were reported to have made bile after revascularization. However, two failed to support life, and retransplantation was required. These cases were classified as instances of primary nonfunction. One of these patients died of hepatic failure; the other was successfully retransplanted three days later. The liver function profiles of the recipients can be found in Table 2. No correlation could be demonstrated between any preharvest donor parameters and eventual organ function, a finding previously noted by others (4).

Hearts. The twelve hearts were transplanted in two centers. Early function was excellent in all cases, indicating that the organ procurement process was satisfactory; subsequent function relates more closely to other variables, such as rejection.

Kidneys. The 34 kidneys were transplanted in eight centers. Two kidneys developed proven hyperacute rejection. Of the remaining 32, 19 functioned immediately, and 13 patients required dialysis during the first postoperative week. Eleven of these 13 eventually gained renal graft function, yielding a total of 30 patients with renal function adequate to support life without dialysis, out of the original group of 34. In nine of the 13 cases of early nonfunction, the contralateral kidney from the donor functioned promptly; there were only two donors in whom both organs failed to function immediately. No correlation was found between any of the donor parameters and subsequent renal graft failure.

Discussion

In final preparation to initiate liver transplantation in New York City and after considerable training in the procedure at the University of Pittsburgh, the Mount Sinai Hospital liver procurement team was formed in January 1987. The team, consisting of surgeons from The Mount Sinai Hospital, received both administrative and technical support from its local procurement agency, the New York Regional Transplant Program. After an initial training period for coordinators and preservationists that involved orientation to acceptable liver donor criteria and specific instruction regarding perfusion and preservation techniques in liver procurement (5), the first harvest took place on January 28, 1987.

TABLE 3
Multiorgan Harvest in the New York Area by The Mount Sinai Hospital Procurement Team

Year	Hearts	Livers
1986	22	18
1987	31	29
1988	46	57

Cardiac retrieval was performed by the team from The Presbyterian Hospital of New York in all but two instances of simultaneous heart and liver harvest. The resultant coordination between the procurement teams allowed them to act essentially as a single unit with respect both to logistics and to surgical techniques. Donor hospitals in the region came to know that the harvesting procedure would be done expeditiously. The resultant enthusiasm is in part responsible for the regional increase in both cardiac and hepatic procurement since the program's inception (Table 3).

The use of the rapid-flush technique for organ harvest has been welcomed by our renal

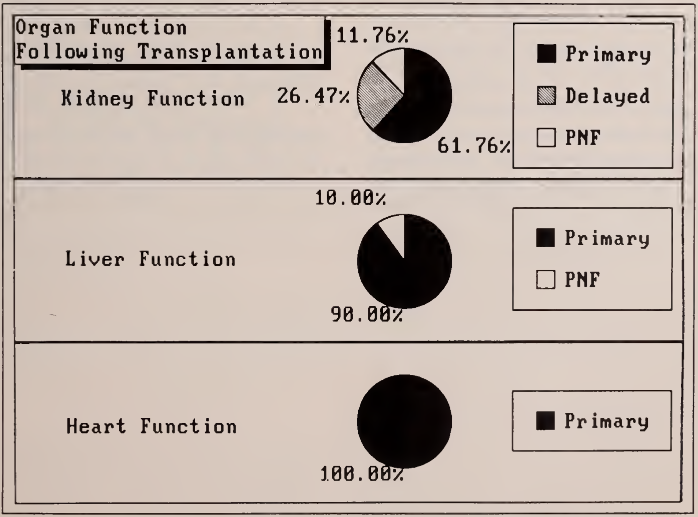

Fig. Functional results of organs retrieved by The Mount Sinai Hospital procurement team.

and cardiac transplant colleagues and coordinators. The speed and efficiency with which the rapid-flush procedure is performed has led to a further streamlining of the process of obtaining organs for transplantation. The overall functional results of the various organs procured in this study were excellent. Bilateral delayed renal graft function was found in only two (10%) of the donors, suggesting that recipient variables such as presensitization and perioperative immunosuppression can have profound effects on early function (6).

Although vital organ retrieval for export has been practiced sporadically throughout the country, to our knowledge this is the first report of a program exclusively dedicated to the procurement of livers for export. By the end of 1986, a transplant team had been assembled at The Mount Sinai Hospital in anticipation of receiving approval from the New York State health commissioner to begin liver transplantation. Final approval was delayed until August 1988; this 21-month interval allowed for the development of the procurement for export program. A close working relationship had been developed between the Mount Sinai Hospital team and other liver transplant programs that fostered trust in each other's experience and expertise and allowed for the promotion of this program.

The University of Wisconsin solution allows hepatic preservation for up to 24 hours (7). It is not difficult to envision an increasingly important role for this type of vital organ procurement and export service in the future. The savings both in transportation costs and in time spent by skilled personnel who would otherwise have to travel long distances to procure their own organs would lead to a reduction in the overall expense associated with organ retrieval (5). Additionally, as in at least five of the cases presented here, logistic considerations at the recipient institutions can preclude organ utilization if a procurement program such as this is not available.

Our successful results support an effort to develop a network of skilled regional procurement teams (5). We have demonstrated that, with close personal communication and an open exchange of data, vital organ procurement for export is a viable option.

Summary

A team providing hepatic procurement in the New York area for export to distant centers was established. Results of transplantation with the organs retrieved were excellent. Savings in both expense and time of skilled personnel were achieved. The future widespread development of similar services is advocated.

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Giant Peptic Ulcers in Patients with Chronic Renal Failure

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Abstract

The clinical characteristics and outcome of patients with peptic ulcer disease (PUD) in association with chronic renal insufficiency were compared with those of patients who had PUD without renal impairment. The number of patients hospitalized with PUD was 150, which represented 1.3% of all hospital admissions to Kingsbrook Jewish Medical Center over the two-year period August 1986 to August 1988. The incidence of PUD among the patients with end-stage renal disease was 2.6%. Mortality was significantly higher in patients with serum creatinine greater than 264 μmol/L (Group A) than in patients with serum creatinine less than 264 μmol/L (Group B) ($p = 0.02$).

A striking finding was the presence of giant (greater than 2 cm in width) gastric and duodenal ulcers and ulcers of the second portion of the duodenum in both groups. The difference in number of giant ulcers in Group A and Group B was statistically significant ($p < 0.001$). Moreover, the patients in Group A had a higher incidence of upper gastrointestinal bleeding and mortality than those in Group B. Group A patients also had a greater need for surgery than Group B patients.

Both groups were predominantly elderly with a mean age greater than 65 years, which may have contributed to the increased incidence of complications and mortality.

A NUMBER of authors have reported an increased incidence of peptic ulcer disease (PUD) in patients with chronic renal failure (1–4), but others have found a low incidence (5, 6).

Upper gastrointestinal hemorrhage has been found to be the cause of death in 3%–7% of patients with moderate to severe renal failure (7). A major cause of upper gastrointestinal bleeding in patients with chronic renal failure (CRF) has been attributed to vascular ectasias of the stomach rather than PUD (8).

Disturbances in serum gastrin (1–4), gastric acid secretion (1, 7, 9–11), the mucosal barrier (12), and the clotting process (13, 14), including platelet alterations, are found in patients with chronic renal failure. These disturbances have been proposed as important factors in the genesis of upper gastrointestinal hemorrhage in these patients. However, Muto et al (15), as well as Kang et al (16), reported that gastric acid secretion is normal to low in patients with chronic renal failure, and that serum gastrin elevation correlated inversely with the range of gastric acid output. Recently, Brady et al (17) have observed that the prolonged gastrin rise after secretin provocation in patients with chronic renal failure may be due to altered renal clearance of gastrin.

The role of alcohol, smoking, and ulcerogenic drugs in upper gastrointestinal hemorrhage was evaluated by Boyle and Johnston (18), who found that these factors were important indicators of outcome in patients with chronic renal failure when compared to a control group with normal renal function. The purpose of this study was (a) to observe the clinical characteristics and outcome of patients with peptic ulcer disease in association with chronic renal insufficiency compared with those who have PUD without CRF, and (b) to ascertain the incidence of PUD among patients

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TABLE 1
Number of Deaths in Patients with PUD Correlated with Levels of Serum Creatinine

Serum creatinine level	No.	Deaths No. (%)	*p* value
<132 μmol/L	118	18 (15%)	0.85
132–264 μmol/L	22	3 (13.6%)	
Subtotal	140	21 (14.9%)	0.02
>264 μmol/L	10	5 (50%)	
Total	150	26 (17.3%)	

with CRF undergoing maintenance hemodialysis treatments.

Methods

The clinical records of all admissions to the hospital with confirmed diagnosis of peptic ulcer disease over a period of two years from August 1986 to August 1988 were reviewed. Patients who had underlying gastrointestinal malignancy were excluded from the study. We included only those patients in whom the diagnosis of peptic ulcer disease was confirmed either by fiberoptic endoscopy or roentgenography of the upper gastrointestinal tract, or at the time of surgery.

The patient's age, sex, medication, associated illnesses, level of serum creatinine, alcohol consumption, and smoking history were recorded. In addition, we noted whether the patient's ulcer disease was the admitting diagnosis or developed during the hospital stay.

For each patient a record was made of the location and size of the peptic ulcer ("giant" defined as >2 cm in width, as in Roth et al, 19) the occurrence of gastrointestinal bleeding, the number of units of blood transfused, and the occurrence of peptic ulcer perforations and other complications. Note was also made of whether surgical intervention was required to control bleeding or to repair perforations and whether the patient recovered or death occurred. The statistical analysis of

TABLE 2
Clinical Data, 10 Patients with PUD and Serum Creatinine >264 μmol/L

Pt. no.*	Age/Sex	Serum creatinine (μmol/L)	Renal disease	Associated illnesses	Diagnosis of PUD	Ulcer type	Surgery	Death
1.	60/M	1258.4	Diabetic nephropathy	Coronary artery disease	Primary	Giant prepyloric	+	–
2.	76/M	466.4	Chronic glomerulonephritis	Coronary artery disease	Secondary	Giant 2nd duodenal	+	+
3.	55/F	748	Diabetic nephropaty	ASCVD Cardiac arrhythmias	Primary	Duodenal	–	+
4.	72/F	343.2	Diabetic nephropathy	Hypertension	Primary	Prepyloric	+	–
5.	72/M	387.2	Nephrosclerosis	Hypertension COPD Schizophrenia	Secondary	Giant duodenal	–	+
6.	45/F	1566.9	Membranous glomerulonephritis	Sarcoidosis Hypertension	Primary	Duodenal	–	–
7.	73/M	800.8	Nephrosclerosis	Hypertension Coronary artery disease Mitral valve replaced	Secondary	Giant 2nd duodenal	+	+
8.	75/F	422.4	Chronic glomerulonephritis	Hypertension Congestive heart failure	Primary	Gastric	–	–
9.	64/M	959.2	Amyloidosis	COPD Coronary artery disease	Secondary	Giant 2nd duodenal	+	+
10.	71/F	880	Chronic glomerulonephritis	Hypertension	Primary	Giant duodenal	–	–

+, yes; –, no; 2nd duodenal, second portion of duodenum; COPD, chronic obstructive pulmonary disease; ASCVD, arteriosclerotic cardiovascular disease.

* All patients except 4 and 5 were undergoing long-term dialysis treatments.

the data utilized chi-square analysis with and without correction of continuity.

A total of 11,400 adult patients were admitted to the medical and surgical wards during the two-year study period. A diagnosis of peptic ulcer disease was confirmed by endoscopy, radiology, or surgery in 150 patients (1.3%). These 150 patients were divided into Group A, with serum creatinine greater than 264 μmol/L, and Group B, with serum creatinine less than 264 μmol/L.

Results

Of the 150 patients in our study, 26 died (17.3%). Correlation of the number of deaths with levels of serum creatinine (Table 1) revealed no significant difference in mortality in those patients with serum creatinine levels below 132 μmol/L and those whose serum levels ranged between 132 μmol/L and 264 μmol/L ($p < 0.85$). The overall incidence of renal insufficiency was 21.3% among patients with PUD.

Clinical characteristics were also assessed for the statistical significance of creatinine levels (Tables 2, 3). Among the 10 patients in Group A, 8 were undergoing maintenance hemodialysis treatments. The total number of patients with end-stage renal disease (ESRD) under our care in the two-year period was 310. Since 8 patients among them had PUD, the incidence of PUD among our hemodialysis population was 2.6%.

Of the 2 patients not receiving maintenance hemodialysis, one (patient 5) died of perforation of the duodenal ulcer and associated peritonitis and the other (patient 4) began and was maintained on regular hemodialysis therapy five months after this admission.

The etiologies of the renal disease in the 10 patients in Group A were chronic glomerulonephritis in 4, diabetic nephropathy in 3, nephrosclerosis in 2, and amyloidosis in 1.

Six of the 10 patients had giant peptic ulcers of the duodenum or prepyloric area. Seven of the 10 had hypertension, and 5 had coronary artery disease.

Comparative clinical data of the 10 patients with PUD and serum creatinine greater than 264 μmol/L (Group A) and the 140 patients with PUD and serum creatinine less than 264 μmol/L (Group B) (Table 3) included mean age ± SE of 66.34 ± 3.21 years in Group A vs. 65 ± 1.65 years in Group B. There were 5 deaths in Group A and 21 deaths in Group B ($p = 0.02$). The requirement for blood transfusions in patients with upper gastrointestinal bleeding was significantly greater in Group A than in Group B ($p = 0.01$). Surgery was performed in 5 patients in Group A and in 20 in Group B ($p = 0.01$).

All 150 patients had a normal coagulation profile as measured by normal prothrombin time, partial thromboplastin time, and platelet count. None of the patients in Group A were receiving oral anticoagulants. Heparin was the sole anticoagulant used during the hemodialysis procedure, and this anticoagulant was discontinued when the patients were having gastrointestinal bleeding.

Of the 150 patients with PUD, 8 had giant peptic ulcers, 6 of them in Group A and 2 in Group B ($p < 0.001$). All these lesions involved the duodenum or prepyloric area. With 2 exceptions, the patients with giant ulcers were older than 65 years. The exceptions were 60 and 64 years old.

TABLE 3

Comparative Clinical Data, 150 Patients with PUD, by Serum Creatinine Level

Clinical characteristic	Group A: 10 patients, creatinine >264 μmol/L	Group B: 140 patients, creatinine <264 μmol/L	*p*
Mean age ± SE (yrs)	66.3 ± 3.21	65.7 ± 1.65	NS
Male:female (no.)	5:5	59:81	NS
Blood transfusions (no. pts.)	9	60	0.01
Ulcerogenic drugs (no. pts.)	1	27	NS
Location of ulcers			
Duodenal	9	81	NS
Gastric	1	53	NS
Both	0	2	NS
Marginal	0	4	NS
Unusual ulcers			
Giant	6	2	<0.001
2nd duodenal	3	1	<0.001
Alcohol abuse	0	5	NS
Smoking 1 pack/day	4	36	NS
Surgery	5	20	0.01
Deaths	5	21	0.02
Perforations	3	10	NS
PUD primary DX	6	105	NS
PUD secondary DX	4	35	NS

2nd duodenal, second portion of duodenum.

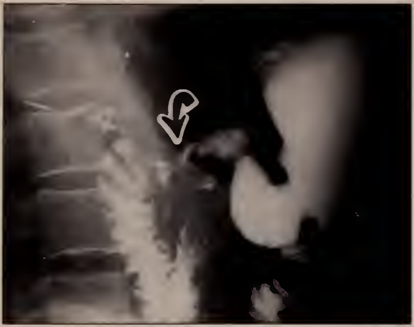

Fig. Case 9. A 64-year-old man with amyloidosis on hemodialysis; giant postbulbar ulcer (arrow).

The intake of ulcerogenic drugs was not significantly different among the two groups. Only 1 patient in Group A received prednisone, 10 mg two times a day, for asthma for four days; 27 patients in Group B were taking nonsteroidal antiinflammatory drugs (Ibuferon, 23 patients; Indocin, 4 patients).

The dialysis patients with PUD were not hypercalcemic. The bath used for dialysis contained Ca^{2+} in a concentration of 2.5 mEq/L.

Discussion

The results indicate that PUD in patients with chronic renal failure and renal insufficiency is frequently complicated by upper gastrointestinal bleeding necessitating blood transfusions, surgical interventions, or both. There is also a high risk of death. Similar results have been reported by others (1–4). The overall mortality of 17.3% found in our study is appreciably higher than that reported by others (20). The reported mortality has varied from 8% to 10%. Pelot and Hollander (20) have emphasized that the varying figures relating to mortality are influenced by demographic characteristics, age, and sex differences. Our population consisted of a large number of patients who were 65 years and older. The age factor may account for the higher mortality in our study. All but 2 deaths occurred in patients 65 years of age or older.

The incidence of PUD among our group with ESRD was 2.6%, which is similar to that reported by Kang et al (16), and appears to be no higher than the incidence in the general population. The 5 deaths among the patients with ESRD occurred in individuals with associated coronary artery disease. The high prevalence of coronary artery disease has been reported previously by others.

Ferrara et al (21), in a retrospective analysis of 50 patients operated on for perforated peptic ulcer, noted that low serum creatinine (less than 132 μmol/L) was the most powerful predictor of survival. We found that the increased mortality of patients with PUD became significant when renal insufficiency resulted in serum creatinine levels greater than 264 μmol/L (Table 1).

Our study included not only patients with perforated peptic ulcer undergoing surgery, but all patients with peptic ulcer disease, and therefore extends the findings of Ferrara et al to this entire population. Furthermore, the need for blood transfusions was appreciably increased in those who had more elevated serum creatinine levels (Table 3). This was especially evident in those requiring maintenance dialysis. Gastrointestinal hemorrhage was the major factor responsible for blood loss sufficient to require blood transfusions.

Although it has been reported that ulcerogenic drugs are an important causative factor in upper gastrointestinal hemorrhage in patients with CRF (18), the number of patients in our study taking ulcerogenic drugs was relatively small. In our opinion, the increased frequency of blood transfusions in patients with severe chronic renal failure may be more satisfactorily explained by factors affecting mucosal integrity and abnormalities of the platelet function induced by uremia.

Our finding that duodenal ulcers are more frequent than gastric ulcers in patients with PUD associated with CRF requiring dialysis is consistent with that of Shepherd et al (3).

What was clearly striking was the presence of giant peptic ulcers and ulcers of the second portion of the duodenum occurring in association with severe CRF (Fig.). In our review of the literature since 1960, this association has not been reported by other investigators. Margolis et al (4) describe the presence of giant folds of gastric and duodenal mucosa in patients with upper gastrointestinal disease and chronic renal failure, which they indicated may be erroneously confused with ulcer craters. No mention of giant ulcers was made by Margolis et al (4). All of the unusual ulcers in our patients were confirmed endoscopically or at the time of surgery. A higher incidence of complications in patients with giant ulcers has been noted by others (22, 23), but its association with renal failure has not been reported to date and warrants further study.

Watson et al (24) reported that giant duodenal ulcers were found to occur frequently in the elderly and that these ulcers had a tendency to bleed severely. Giant gastric ulcers were reviewed by Barragy et al (25), who concluded that medical therapy (H2 blockers and antacids) compared favorably with surgical therapy. However, these authors reported 10 medical failures among 44 nonmalignant gastric ulcers.

In our study, PUD in patients with severe renal impairment was associated with an increased frequency of complications, including bleeding and greater risk of mortality. These considerations suggest that a more aggressive medical and surgical approach to the treatment of these patients is warranted. Additional studies are needed to confirm the association of giant peptic ulcers and chronic renal failure.

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Cystic Neoplasms of the Pancreas

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Abstract

Cystic neoplasms of the pancreas can be easily misdiagnosed and mistreated by the surgeon unfamiliar with the pathology, natural history, and operative strategy specific to these uncommon tumors. The authors have treated nine patients over a seven-year period involving four cystadenocarcinomas, two mucinous cystadenomas, two serous cystadenomas, and one solid and papillary epithelial tumor. Our experience illustrates the inaccuracies in both clinical and pathologic diagnosis. Suspected cystic neoplasms are optimally managed by resection. Their slow growth and late metastasis permits curative surgery after a previous drainage or bypass procedure. An aggressive surgical approach is therefore warranted, and multimodal treatment with radiation and chemotherapy may be clinically applicable to large, invasive cystadenocarcinomas.

CYSTIC neoplasms of the pancreas are uncommon tumors that account for 10%–15% of pancreatic cystic lesions (1). Although few cases have been reported in the literature, it is likely that misdiagnosis has resulted in a low estimate of the incidence of these neoplasms.

Serous and mucinous cystadenomas are two distinct groups of pancreatic cystic lesions. Serous cystadenomas are also termed microcystic cystadenomas. Composed of multiple small cysts lined by cuboidal epithelium, microcystic cystadenomas contain little or no mucin, and are considered benign. Mucinous or macrocystic cystadenomas are characterized by large cysts lined with columnar cells and contain mucoid or hemorrhagic fluid. Cystadenomas of the mucinous type have malignant potential, and seemingly benign lesions may be found to harbor foci of dysplastic or frankly neoplastic cells (2, 3).

Cystadenocarcinomas have gross and histologic features resembling the mucinous cystadenoma. These two lesions may represent a single pathologic entity displaying variable degrees of malignancy (4, 5). Compagno and Oertel (6) have suggested the term mucinous cystic neoplasm to distinguish this potentially malignant lesion from the benign serous variety.

Solid and papillary epithelial neoplasms are rare cystic tumors of the pancreas. These lesions have many pathologic features in common with mucinous cystic neoplasms. However, solid and papillary epithelial tumors may be distinguished from mucinous cystic neoplasms because they lack true papillae and do not contain large amounts of mucin.

Most commonly found in women, cystic tumors of the pancreas are indolent and slow growing and can attain considerable size. These tumors can occur in any portion of the pancreas, but occur most frequently in the body and tail (6). Abdominal pain is the most common symptom. In the unusual case, encroachment on adjacent structures may result in obstructive jaundice or bleeding gastroesophageal varices (7, 8). The discrimination of cystic neoplasms from pancreatic pseudocysts may be difficult. Several studies have found cystic pancreatic neoplasms associated with elevated carcinoembryonic antigen levels

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(9, 10), although no consistent marker for these lesions has been identified. Computed tomography is the most helpful diagnostic study; however, angiography can aid in defining these tumors (11, 12).

Total excision is the preferred treatment for all cystic neoplasms and should afford cure of benign lesions. Hodgkinson et al. calculated a 68% five-year survival after resection for cystadenocarcinoma (13). Drainage is not appropriate therapy because these tumors tend to recur if not completely excised. The use of radiotherapy and chemotherapy as adjuvant treatment for large, regionally invasive cystadenocarcinomas has rarely been described.

Case Reports

We have treated nine patients with pancreatic cystic neoplasms over the previous eight years at Cedars-Sinai Medical Center (Table). Seven patients were female, and six were in their fifth decade of life. There were six mucinous neoplasms, of which two were benign. There were also two serous cystadenomas, and one solid and papillary epithelial tumor. Several of these cases have features which merit special consideration:

Case 3, a 29-year-old black woman, sustained blunt abdominal trauma in an automobile accident. Ten weeks following her injury, an 8-cm cystic lesion in the tail of the pancreas was noted on computed tomography during studies for abdominal pain. The preoperative diagnosis was traumatically induced pseudocyst. Resection with splenic preservation was performed, yielding an unsuspected solid and papillary epithelial tumor.

Case 7 is a 48-year-old Korean man who underwent celiotomy for a large upper abdominal mass causing duodenal and transverse colon obstruction. Gastrojejunostomy and ileotransverse colostomy were performed. A diagnosis of sarcoma was made by frozen section, although later histologic examination revealed only inflammation, without evidence of malignancy. Reevaluation seven months postoperatively demonstrated an elevated carcinoembryonic antigen (CEA) level of 40 ng/ml. Computed tomographic needle biopsy was performed showing only inflammatory tissue. Within two months the CEA level had risen to 80 ng/ml associated with weight loss. Exploration one year later revealed a 25-cm mass emanating from the head and body of the pancreas. Safe resection was deemed impossible, and the operation was terminated after obtaining multiple biopsies which demonstrated cystadenoma. After celiotomy, a CEA level of 130 ng/ml was obtained. The patient underwent external beam radiotherapy delivering 4400 rads and two courses of 5-flourouracil. The tumor decreased in size and the CEA fell to 20 ng/ml. At this point, the tumor was successfully removed by pancreaticoduodenectomy with subtotal colectomy, partial gastrectomy, and segmental small bowel resection. The final pathology revealed a cystadenocarcinoma. The CEA level was 5 ng/ml one month after resection.

TABLE

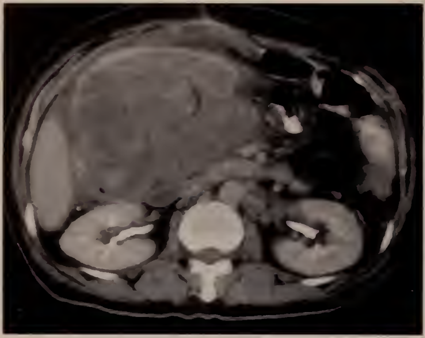
Cystic Neoplasms of the Pancreas, Nine Cases

Pt. no.	Sex	Age yrs	Diagnosis	Operation	Postop follow-up
1	F	49	cystadenocarcinoma	Distal pancreatectomy and splenectomy	Well after 5 years
2	M	49	cystadenocarcinoma	Total pancreatectomy	Well after 3 years
3	F	29	Solid and papillary epithelial tumor	Distal pancreatectomy	Well after 2 years
4	F	70	Serous cystadenoma	Distal pancreatectomy and splenectomy	Well after 2 years
5	F	47	Cystadenocarcinoma	Distal pancreatectomy and splenectomy	Well after 1 year
6	F	48	Mucinous cystadenoma	Distal pancreatectomy	Well after 5 years
7	M	48	Cystadenocarcinoma	Whipple procedure, subtotal colectomy, partial small bowel resection, partial gastrectomy	Well after 2 years
8	F	49	Mucinous cystadenoma	Subtotal pancreatectomy and splenectomy	Well after 2 years
9	F	69	Serous cystadenoma	Total pancreatectomy	Well after 4 years

Case 8, a 49-year-old white woman underwent internal drainage of a "pseudocyst" 18 years before our examination. The mass reappeared, and external drainage was performed. One year later, computed tomography revealed a 12 × 9 cm multiloculated mass in the body and tail of the pancreas associated with varices (Fig. 1). The lesion, which proved to be a mucinous cystadenoma, was removed by subtotal pancreatectomy and splenectomy (Fig. 2).

Discussion

It is imperative to distinguish pancreatic pseudocysts from true cystic neoplasms because



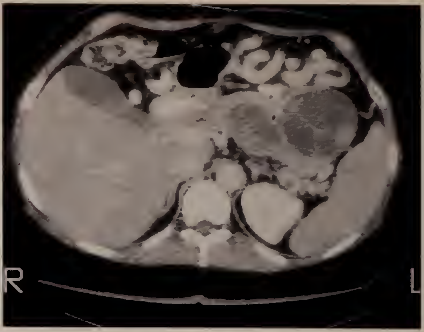


Fig. 1. Left Abdominal CT showing large multiloculated cystic mass with internal septae in body and tail of pancreas. Note varices associated with this mass. **Fig. 2. Right** Subtotal pancreatectomy and splenectomy enabled complete resection of this mucinous cystic cystadenoma.

the treatment for these two lesions is different. The majority of pancreatic pseudocysts are of inflammatory or traumatic origin and are amenable to drainage. The cystic neoplasm may be difficult to distinguish from a pseudocyst but requires total excision.

Warshaw and Rutledge (14) suggest several criteria to help differentiate a cystic neoplasm from a pseudocyst. Pseudocysts lack an epithelial lining and usually contain fluid that is high in amylase. Communication with the pancreatic duct system is found in a majority of pseudocysts and not in cystic neoplasms. Multiple cysts and internal septae are frequently seen in cystic neoplasms but not in pseudocysts (14).

Angiography of cystic neoplasms usually demonstrates a vascular mass with large feeding vessels and a tumor blush. These features are not characteristic of pseudocysts.

Computed tomography shows a lobulated pancreatic mass and delineates the solid and cystic components of the neoplasm well. "Sunburst" calcifications, which are seen in a minority of cystic neoplasms, are more frequently visualized by this technique than by conventional radiographs (15).

We agree that information gained from computerized tomography, angiography and ERCP may be of value in obtaining the diagnosis; however, we have been impressed with the limitations of these studies rather than their reliability in providing an accurate diagnosis.

In our series, CEA was measured for three patients and was elevated in one case of a cystadenocarcinoma. Changes in the CEA level were directly correlated with therapeutic interventions. Several previous reports describe elevated CEA levels in both the cystic fluid and the serum of patients with cystadenocarcinoma (9, 10). It is clear that CEA is not elevated in all patients with cystadenocarcinoma, but it should be measured when a diagnosis of pancreatic cystic neoplasm is entertained. If high levels are found, the likelihood of malignancy should be suspected.

When a suspected pseudocyst is drained internally, a biopsy of the cyst wall and aspiration of the cyst fluid for amylase and cytologic study should be performed. Digital evaluation of the cyst cavity may reveal loculations or solid areas suggestive of a neoplastic process. Frozen section can be helpful when the operative findings suggest tumor. The presence of epithelial cells makes a diagnosis of pseudocyst doubtful.

We feel that except under extenuating circumstances all cystic lesions in the tail of the pancreas are optimally treated by resection. Cystic neoplasms anywhere in the pancreas should be resected. Internal drainage may convert a sterile cyst to an infected one, fail to relieve symptoms, and leave behind a curable carcinoma.

Failure of a pseudocyst to collapse within several weeks of drainage indicates a possible misdiagnosis. The slowly progressive nature of the cystic neoplasm permits curative resection after a drainage procedure. Palliative surgery to relieve intestinal or biliary obstruction is indicated when metastases or coexisting illness contraindicates resection.

Advanced cystandenocarcinomas may infiltrate adjacent structures, but distant metastases occur late. Large, locally invasive tumors should therefore not be dismissed as inoperable without a thorough evaluation. For such cases, preoperative workup may require computed tomography, visceral angiography, gastrointestinal radiographs, and ERCP. When preoperative assessment or findings at celiotomy contraindicate resection, we suggest consideration of combination radiotherapy and chemotherapy. Although the role of these adjuvant modalities has not been established, we have witnessed an encouraging result in one patient (case 7).

Summary

Neoplastic cysts of the pancreas are rare and may be difficult to diagnose prior to resection. Confusion with the more common pseudocyst can result in inappropriate therapy. Cystic lesions in the tail of the pancreas are best excised. Drainage of the cystic neoplasm is inadequate since curative resection is usually possible. When misdiagnosis occurs, curative resection can still be performed.

Since metastases occur late, even regionally invasive cystadenocarcinomas can be successfully treated by en bloc resection of involved viscera. In selected cases radiotherapy and chemotherapy may have an adjuvant role in the surgical treatment of these tumors.

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Internal Rectal Prolapse:

Rubber-Band Ligation as Treatment for a Neglected Disease

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Abstract

Internal rectal prolapse was diagnosed in 21 patients with signs and symptoms consistent with this syndrome. They all underwent rubber-band ligation of the excess mucosa—2.2 procedures per patient on average. Eight patients became asymptomatic and 13 significantly improved clinically. Six patients, in spite of the clinical improvement, had rectoscopic evidence of recurrence. No side effects or complications were noted.

Internal rectal prolapse has to be considered in the differential diagnosis of anorectal syndromes. Rubber-band ligation is a safe, simple procedure, leading to resolution of symptoms, and may prevent progression to total rectal prolapse.

Internal rectal prolapse occurs when a portion of the rectal mucosa, in most cases about 6–8 cm above the anal verge on the anterior wall, becomes redundant and extrudes toward the anal canal, without protruding through the anus. This interesting phenomenon was first described in 1903 (1). Many cases have been described since (2–6), but there is still no agreement concerning incidence, etiology, pathogenesis, or therapy. It is not known whether the entity is independent or just a partial mucosal prolapse which can lead to a total rectal prolapse.

Twenty-one cases of internal rectal prolapse, treated by rubber-band ligation of the mucosal excess, are presented.

Patients and Methods

Twenty-one patients with internal rectal prolapse were assessed by proctosigmoidoscopy and treated by rubber-band ligation in our proctology clinic. The diagnosis was established on clinical and proctosigmoidoscopic grounds (7). The proctoscopic examination included slow withdrawal of the instrument while the patient was performing a Valsalva maneuver. A careful clinical evaluation and a conventional barium enema study were performed before the ligation, and the patients were followed up clinically at 3-month intervals thereafter. At the last follow-up proctoscopy was offered with no relation to the clinical situation. Eight patients underwent the examination.

Results

Twenty-one patients with internal rectal prolapse were treated with rubber band ligation. There were 12 women and 9 men. The average age was 62 years (range: 36–87); only 5 patients were below the age of 50. Constipation was the most common clinical feature (Table 1). In 13 patients (62%) additional abnormalities were found on proctosigmoidoscopy (Table 2). Previous surgical procedures (gynecologic, urologic, or proctologic) had been performed on 15 patients (71%) (Table 3). Six patients received other forms of therapy—5 had medical treatment and 1 underwent rectopexy. An average of 2.2 ligations and 3.2 proctosigmoidoscopies was performed in each patient.

All the patients were available for followup (Table 4), the average duration of which was 13.7 months (range: 2–48). In 8 patients rectoscopy was performed at the last follow-up, with normal-appearing mucosa in 2 and recurrence of the prolapse in 6. Eight patients were found to be

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asymptomatic, and clinical improvement was reported by the other 13. Barium enema revealed diverticulosis in 3 patients and was normal in the remainder.

Discussion

Internal rectal prolapse (IRP) is frequently missed on regular sigmoidoscopy, unless it is specifically looked for. This explains the lack of accurate data on prevalence.

Proctoscopy in the Sims position, without air insufflation, is the best way to demonstrate IRP. Redundant, loose mucosal folds can be seen to prolapse into the instrument while the patient is straining and can be grasped by forceps and brought to the anal level (ensuring that only the mucosal layer is partially prolapsed). Many times the prolapse starts from the anterior rectal wall, where the mucosa is sometimes edematous or eroded.

The etiology and pathogenesis of IRP are not clear, nor is its clinical spectrum. There is an association of IRP with solitary rectal ulcer syndrome (SRUS), colitis cystica profunda, and the descending perineal syndrome (7–17). IRP was demonstrated in 16% to 100% of SRUS patients, depending on whether it was thoroughly looked for (7, 9, 12, 13).

The pathogenesis of these syndromes can be explained by abnormalities of pelvic floor muscle motor activity. Anorectal angle, according to lateral radiographs of the pelvis in healthy volunteers, was found to be 92.2° at rest position, 87.4°, on squeezing, and 107.5° on straining (17). The mucosa of the anterior wall is opposed to the inlet of the anal canal and plays the role of a flap valve. Electromyographic studies in patients with SRUS revealed an abnormality of the pelvic floor musculature in that the normal relaxation of the puborectalis muscle during straining is replaced by overactivity (16). This may lead to the anterior wall being forced against the contracting muscle during straining and thereby prolapsed or

TABLE 1
Clinical Features (21 Patients)

Symptoms and signs	No. patients
Constipation	12 (57%)
Incomplete evacuation	10 (48%)
Rectal bleeding	7 (33%)
Abdominal pain	7 (33%)
Anorectal pain	6 (29%)
Tenesmus	5 (24%)
Anal discharge	3 (14%)

TABLE 2
Results of Proctosigmoidoscopy (21 Patients)

Pathology	No. patients
Internal rectal prolapse	21
Internal hemorrhoids	10
Anal fissure	3
Proctitis	2
Rectal polyp	1

TABLE 3
Previous Surgical Procedure (15 Patients)

Procedure	No. patients
Urologic	
Prostatectomy	3
Gynecologic	
Hysterectomy	3
Ant. colporrhaphy	1
Proctologic	
Hemorrhoidal ligation	5
Hemorrhoidectomy	2
Post. anal repair	1
Anal dilatation	1
Other	
Colonoscopic polypectomy	2
Excision of pilonidal sinus	1

TABLE 4
Last Follow-Up

Pt. no.	Proctoscopy		Clinical evaluation	
	Prolapse	Normal	Improved	Asymptomatic
1		+		+
2	+		+	
3	+		+	
4		+	+	
5				+
6			+	
7				+
8	+		+	
9	+		+	
10			+	
11	+		+	
12				+
13				+
14				+
15	+		+	
16			+	
17				+
18			+	
19			+	
20				+
21			+	
Total	6	2	13	8

traumatized. Another factor that dictates the severity of the lesion or the development of the pelvic floor descent syndrome is the tonicity of the sphincters and supporting ligaments of the rectum (8, 16, 17).

Ripstein considers IRP to be the first stage in the natural history of complete rectal prolapse (5). This view was confirmed by three case reports (2, 3). None of our patients progressed from IRP to complete rectal prolapse, but perhaps mean follow-up duration of 13.7 months is too short to rule out this progression.

IRP may cause many symptoms (Table 1) and mimic other prevalent syndromes. As a matter of fact, most of our patients were previously diagnosed as having laxative abuse, spastic colon, or psychoneurosis. The most common symptoms were constipation and incomplete evacuation. Some patients regularly practiced manual finger evacuation. Rectal bleeding was not so frequent and always was found when other pathology was revealed by proctoscopy.

The treatment of IRP is still controversial. Ripstein had good results with the "sling operation" in 11 of 12 patients with IRP (5), but this is a major surgical procedure. Rubber-band ligation of the prolapsed mucosa is a safe and painless procedure. This procedure causes sloughing of the apex of the invaginating mucosa and the adherence of its base to the muscularis. All our patients became asymptomatic or had a significant clinical improvement, but proctoscopic evidence of recurrence was demonstrated in 6 of 8 patients who underwent proctoscopy on the last follow-up. We cannot explain this discrepancy between clinically significant improvement and recurrence, but we suspect that the length of the mucosal prolapsed fold has a role. The procedure was easily performed and could be repeated until successful resolution of symptoms. No side effects or complications occurred in an average follow-up of 13.7 months.

We conclude that internal rectal prolapse must be considered in the evaluation of patients with rectoanal and abdominal complaints. Rubber-band ligation is recommended as a therapeutic approach, even though repeated sessions are needed in most instances.

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Cystometric Evaluation of Vesical Endometriosis before and after Hormonal or Surgical Treatment

MARTIN S. GOLDSTEIN, M.D., AND MICHAEL L. BRODMAN, M.D.

Abstract

Subjective patient complaints as they relate to bladder endometriosis have been well reported. Objective findings have been lacking. The case reported on demonstrates the cystometric finding of a small-capacity irritable bladder in a patient with vesical endometriosis. It further demonstrates the improvement of these findings following surgical resection of endometrioses and hormonal therapy using danazol.

Bladder endometriosis was first reported by Judd in 1921 (1). This entity now represents 1.1% (2) of all cases of endometriosis and 84% of cases involving the urinary tract (3).

The classic constellation of symptoms associated with endometriosis includes dysmenorrhea, pelvic pain, dyspareunia, menstral dysfunction, and infertility. However, depending on where the endometriosis implants, a variety of other problems can arise. Bladder endometriosis can be associated with hematuria, pain, and urethral vesical dysfunction.

Treatment for endometriosis has included local excision, partial bladder resection, oophorectomy, and hormonal therapy. Hormonal therapy using danazol has been shown to alleviate the symptoms associated wiith endometriosis. Its success in alleviating pain, dysmenorrhea, dyspareunia, and infertility has been well documented (4–6). When used in bladder endometriosis, it improves the subjective complaints of dysuria, hematuria, and lower abdominal and pelvic pain (7). Cystometric evaluation in such cases, however, has been lacking. The purpose of this report is to document the cystometric effects of endometriosis on the bladder as well as the changes in bladder function associated with hormonal and surgical therapy.

Case Report

A 32-year-old, gravida 0 woman in 1976 had complaints of frequency every hour, nocturia 3–4 times a night, urgency, and urge incontinence. The symptoms developed at age 20, but were improved during 6 years of oral contraceptive usage, which ended in 1974. The medical history was noncontributory other than for the symptoms described.

On initial examination, general and neurologic findings, including deep tendon reflexes, perineal sensation, and vibratory sensation, were normal. Gynecologic examination demonstrated excellent vaginal supports and no posterior urethral rotation or demonstrable stress incontinence. The uterus was normal in size and anteverted.

In the next 7 years, the patient was followed up by one of the authors (MSG) in consultation with several urologists. Urologic evaluation disclosed a normal intravenous pyelogram and cystoscopic findings. Urethral dilatation and hydraulic bladder distention provided no symptomatic improvement. Cystometrics performed Dec.

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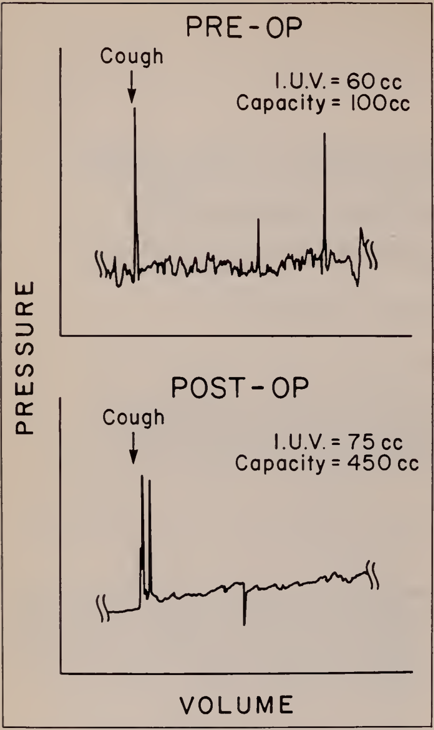

Fig. 1. Cystometrograms before and after surgery. Note decrease in irritability as well as increase in bladder capacity from 100 ml to 450 ml following surgery. I.U.V., initial urge to void.

9, 1981 (Fig. 1) revealed uroflow rate of 15 ml/sec, residual urine of 20 ml, a supine bladder capacity of 200 ml with bladder instability, and a standing capacity of 100 ml. Maximum closing pressure of the urethra was 100 cm of water.

Pharmacologically, Dibenzyline, Ditropan, pyridium, urised, Probanthine, and Imipramine were prescribed in appropriate dosage, with no relief of the urinary symptoms.

On examination in December 1982 the patient had a normal-sized uterus. Three months later, in March 1983, examination revealed a 14-week-sized uterus, the change due to rapidly enlarging fibroids. Cystometrics performed on May 2, 1983 demonstrated initial urge to void of 60 ml, standing capacity of 100 ml, with maximum closing pressure of 70 cm of water. Preoperative intravenous pyelogram was normal. Cystoscopy showed normal bladder mucosa and urethra. An exploratory laparotomy and myomectomy was performed on May 27, 1983. The bladder was found to be duplicated and adherent to the lower uterine segment by a 4-mm endometriotic nodule. The endometriosis was excised from the bladder serosa and muscularis without entering the bladder mucosa. The cul-de-sac contained significant endometriosis of the uterosacral ligaments, which was cauterized. The patient had an uneventful postoperative course and was discharged on the eighth postoperative day.

The patient noted dramatic improvement in bladder symptoms at the time of hospital discharge. Nocturia, urgency, and urge incontinence had completely resolved. Urinary frequency diminished to every 3–4 hr. Cystometric evaluation on September 28, 1983 (Fig. 1) showed flow rate of 25 ml/sec, initial urge to void of 75 ml, a standing bladder capacity of 450 ml with no bladder instability, and a maximal urethral closing pressure of 90 cm of water.

Bladder function remained normal until November 1984, when the patient noted a gradual return of nocturia, frequency every 1–2 hr, severe urgency, and urge incontinence. Urine culture was negative. Cystometric examination on February 11, 1985, showed a urinary flow rate of 20 ml/sec, 15 ml urinary residual, initial urge to void at 50 ml, and a bladder capacity of 120 ml with bladder instability. Maximum urethral closing pressure was 100 cm of water (Fig. 2).

In view of the histologically proven endometriosis, a course of danazol, 200 mg four times a day, was started and maintained for 3 months. The patient had total remission of symptoms. Cystometric evaluation on May 13, 1985, after danazol therapy demonstrated a bladder capacity of 370 ml with no bladder instability. The patient was still asymptomatic one year later. No symptoms of endometriosis such as dysmenorrhea were ever described by the patient. Hematuria was never identified.

Discussion

Previous reports have documented improvement in subjective patient complaints arising from bladder endometriosis after surgical and medical therapies. Those complaints include pain, dysuria, and hematuria. This case documents the objective physical findings of bladder endometriosis using cystometrics and its improvement following medical and surgical management.

In this case, the patient had complaints of

	PRE OP 5/2/83	POST OP 9/28/83	RECURRENT BLADDER ENDOMETRIOSES 2/11/85	DANOCRINE × 3 MONTHS 5/13/85
Nocturia	× 4	0	× 2	0
Frequency	q ½ hr	q 3½ hr	q 1 hr	q 3 hr
Urgency	+ +	0	severe	minimal
Urge incont.	+	0	+	0
Capacity	100 cc (standing)	450 cc	120 cc	370 cc
Instability	+ + +	+	+ +	+
U.P.P.	70 cm	90 cm	100 cm	100 cm

Fig. 2. A comparison of the subjective patient complaints (nocturia, frequency, and urgency) and objective cystometric findings (urge incontinence, capacity, and instability in urethral pressure profile) pre- and post-operatively as well as pre- and post-danazol treatment. U.P.P., urethral pressure profile; + +, severe; +, moderate.

urgency and frequency that were confirmed by the urodynamic finding of decreased bladder capacity and instability. The endometrioses did not extend into the mucosal layer of the bladder. A possible mechanism of action for bladder irritability is the result of a local irritative focus in the muscularis layer.

This case demonstrates that endometriosis in the bladder can cause irritability and reduced bladder capacity documented by cystometrics. The surgical excision of endometriosis clearly was successful in increasing bladder capacity and at the same time improving all symptoms of bladder irritability. Danazol, a derivative of a synthetic 17-alpha-testosterone, has been shown to reduce endometriosis-related complaints. More specifically, one case study showed that it can be used to reduce urinary tract complaints (7). Our patient demonstrated subjective and objective improvement in bladder function. As a result of endometriosis, this patient had a reduction of bladder capacity and increased irritability. Both surgery and danazol were effective in improving the problem.

The physician should be aware that the initial symptoms of endometriosis can be urologic complaints of hematuria, dysuria, irritability, and reduced bladder capacity. Patients with unexplained urinary complaint of frequency, urgency and nocturia associated with a small-capacity unstable bladder, unresponsive to conventional parasympatholytic therapy, should be evaluated for bladder endometriosis as a possible cause of these findings. Medical and surgical treatments of endometriosis can be used successfully in treating symptomatic bladder endometriosis. A prospective study will be needed to determine whether this is in fact an incidental finding or a reproducible problem.

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Delayed Air Embolism during Vascular Surgery

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Abstract

Air embolism occurred in a 25-year-old patient undergoing surgery for reconstruction of the subclavian vein. Air embolism probably occurred twice, the second time at about an hour after closure of the vein. The cause of this delayed air embolism is discussed. We conclude that capnographic monitoring for air embolism is advisable whenever surgery is performed on a patient in the half-sitting position, and that inserting a central venous catheter to facilitate removal of the air in the event of massive air embolism may be wise.

Air embolism during general surgery has rarely been described. In this report we present the case of a patient with multiple air embolism during and after reconstruction of the subclavian vein.

Case Report

A 25-year-old woman was admitted for reconstruction of the right subclavian vein. Four years before, she had suffered a thrombosis of this vein, which was treated with fibrinolytics. Subsequently she had a partial resection of the first rib.

Preoperative physical examination of the patient showed no abnormalities other than a swollen right arm with venodilatation.

Laboratory tests and pulmonary function tests were normal. The current phlebographic study showed a total block of the subclavian vein with partial obstruction of the collateral circulation. The preoperative electrocardiogram showed an incomplete right bundle branch block. The chest roentgenogram was normal.

One hour before induction of anesthesia, intramuscular premedication consisting of atropine 0.5 mg, droperidol 5 mg, and fentanyl 100 μg was given. After induction of anesthesia with fentanyl 350 μg, thiopentone 250 mg, and droperidol 17.5 mg, and muscle relaxation with pancuronium 7 mg, the patient was intubated and controlled ventilation was instituted. End-tidal carbon dioxide concentration was monitored with an off-stream infrared gas analyzer (capnograph). A gastric tube and a urinary catheter were inserted.

Because the operation was performed with the patient in the half-sitting position, a central venous catheter was introduced. The catheter was inserted through the anticubital vein by the technique of Seldinger. Further hemodynamic monitoring consisted of electrocardiography, finger plethysmography, and direct intra-arterial blood pressure monitoring. Three hemodynamic parameters and the end-tidal CO_2 concentration (capnogram) were recorded with a polygraph.

After midline sternotomy, the right subclavian vein was explored. The operation proceeded uneventfully for three hours. The remnant of the first rib showed an exostosis compressing the subclavian vein. Seventy-five milligrams of heparin was given intravenously before the subclavian vein and the brachial vein were opened. The surgeon performed a thrombectomy and a patch was sutured in the subclavian vein.

At the time the vein was flushed and before the vein was closed, a fall of end-expiratory CO_2 concentration was noticed in the capnogram (Fig. 1). Arterial blood pressure and central venous

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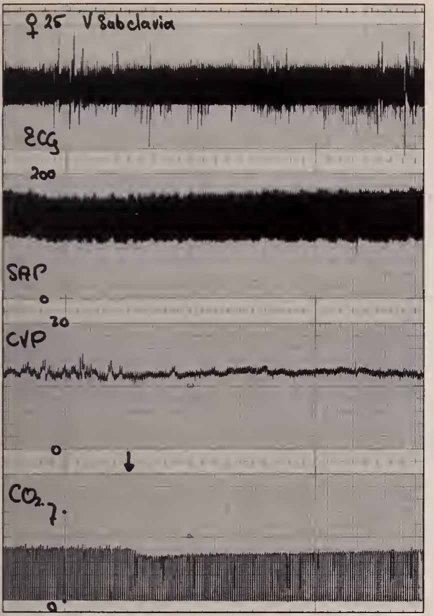
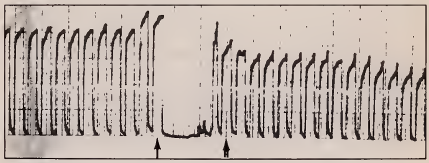


Fig. 1. Left Polygraphic recording of electrocardiogram (ECG), systemic arterial blood pressure (SAP), central venous pressure (CVP), and end-tidal CO_2 concentration (CO_2) during first air embolism. In capnogram, typical wash-out curve is seen. There is no change in arterial blood pressure and central venous pressure. Fig. 2. Below Recording of end-tidal CO_2 concentration before and during second (long-lasting) period of air embolism, occurring just after brief disconnection (arrow) of the ventilator. Reconnection is indicated by double arrow.



pressure showed little or no change. During flushing of the proximal and the distal part of the vein, a good flow of blood appeared and no clots or thrombi were seen. At that moment no hemodynamic or capnographic changes occurred and the operation was continued.

The venous circulation of the right arm was restored. The operation was continued with the resection of the remnant of the first rib. Half an hour afterward (80 minutes after the first change in end-tidal CO_2 concentration) a second, more pronounced, longer-lasting and recurring fall in end-tidal CO_2 concentration occurred (Fig. 2; time points at which polygraph stopped and then started are shown on figure), accompanied by a decrease of 30 mm Hg in arterial blood pressure, a rise in central venous pressure, and a ventricular arrhythmia.

Five milliliters of air was aspirated through the central catheter. Nitrous oxide was discontinued and the patient was ventilated with 100% oxygen. Anesthesia was maintained with enflurane 0.6% and increments of fentanyl. The patient was placed in head-down position. Gradually the end-tidal CO_2 concentration and the circulatory parameters returned to normal, and the operation was completed without further complications.

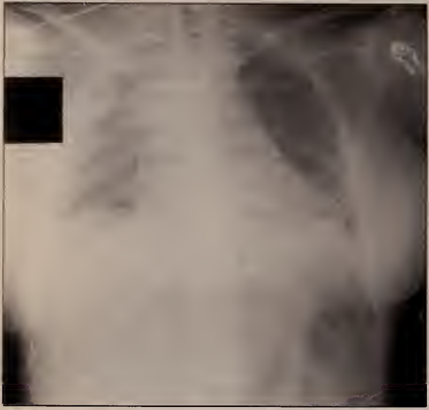
Blood gas analysis and acid-base measurements were performed several times during the operation. Alveolar-arterial Po_2 difference, intrapulmonary shunt fraction, and volume of dead space were calculated, with the aid of the "short-cut method" of Fournier and Major (1) (Table).

TABLE

Preembolism and Postembolism Circulatory and Ventilatory Parameters

	Air embolism 1		Air embolism 2		
Parameter	Before	During/ after	Before	During	After
Heart rate (beats/min)	75	76	80	109	90
Systolic/diastolic arterial BP (mm Hg)	164/88	168/98	176/88	145/70	155/80
Central venous pressure (mm Hg)	18	19	19	20	17
End-tidal CO_2 concentration (volume percent)	4,1	3,4	4,1	2,3	4,0
Arterial CO_2 pressure (mm Hg)	36	38	38	34	30
Alveolar-arterial difference in oxygen tension (mm Hg)	58	68	104	180	286
Intrapulmonary shunt fraction (%)	9,2	8,6	16	13	23
Volume of dead space (mL)	94	137	138	159	176

BP, blood pressure



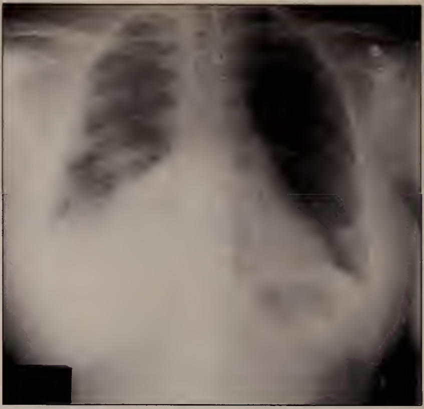


Fig. 3. Left Postoperative chest roentgenogram: pleural fluid in right hemithorax, signs of pulmonary edema, possible atelectasis of lower lobe of right lung. Fig. 4. Right Chest roentgenogram 3 days postoperatively: hazy shadow disappeared; atelectasis of lower lobe of right lung and small atelectasis in left lower lobe are seen.

It was decided to continue artificial ventilation postoperatively for 24 hours. The postoperative chest roentgenogram (Fig. 3) showed pleural fluid in the right hemithorax and a hazy shadow over both lungs. The 12-lead electrocardiogram was unchanged. On the following day the patient was weaned from the ventilator and extubated in good condition. The chest roentgenogram showed decrease of the pleural fluid in the right hemithorax, a large area of atelectasis in the lower lobe of the right lung, and a smaller area of atelectasis in the lower lobe of the left lung; the hazy shadow had nearly disappeared (Fig. 4). Two weeks postoperatively the patient left the hospital in a good condition.

Discussion

Air embolism is a well-known complication occurring during posterior fossa surgery and operations on the cervical spine performed with the patient in the sitting position (2). The complication may appear in general surgery, during cardiopulmonary bypass (3), and in total hip arthroplasties (4). Small air embolisms usually remain undiagnosed unless extensive monitoring is used.

The patient presented in this report developed symptoms of air embolism during reconstruction of the right subclavian vein. The patient was at risk for air embolism because of the semi-sitting position during the operation while the venous circulation was to be opened. In the semi-sitting position the pressure in the veins of the head and neck, and even the pressure in the superior caval vein, can be subatmospheric (5, 6). When the pressure in the vein is subatmospheric and the vein is opened, air may enter the circulation, and air embolism occurs. Realizing this risk, we paid special attention to diagnostic and therapeutic measures during the procedure.

The capnograph (end-tidal CO_2 concentration measurement and recording) is known to be a reliable monitor for the detection of air embolism (7). Use of the capnograph as an air embolism monitor is based on the assumption that embolized air will rapidly move into the pulmonary circulation. This results in transient arteriolar and capillary obstruction with local reflex vasoconstriction and opening of shunts, resulting in ventilation-perfusion mismatch. In cases of air embolism a typical wash-out curve occurs, consisting of an abrupt reduction in the concentration of the end-tidal CO_2 concentration with a gradual recovery (8). In dogs a good correlation was demonstrated between the size of the air embolism and the quantitative fall in end-tidal CO_2 concentration (9).

The clinical use of capnography proved to be quantitatively comparable to invasive pulmonary artery pressure monitoring (10, 11). A central venous catheter was inserted, not for diagnostic purposes, but to be able to aspirate air from the superior vena cava in case of massive air embolism. Central venous pressure monitoring for the detection of air embolism is of limited value (12). Indeed, in the patient reported on here, only a small change in central venous pressure occurred. However, we aspirated air, confirming the diagnosis.

A specific monitor for the detection of air embolism is Doppler ultrasound detection. A precordial Doppler ultrasound monitor was not used, for it was impossible to place a precordial transducer with this procedure. A transesophageal Doppler monitor was not available.

A typical fall in end-tidal CO_2 concentration occurred twice in this patient. The first episode occurred without hemodynamic changes, so the capnographic changes were the only sign of air embolism. The second episode was accompanied by blood pressure fall, rise in central venous pressure, and a ventricular arrhythmia. Striking changes were seen in the single CO_2 curves: an irregular plateau typical of ventilation-perfusion mismatch (13). After the presumed embolism, the intrapulmonary shunt and dead-space ventilation were increased.

Remarkably, the second episode of air embolism occurred about one hour after closure of the vein. It is unlikely that this second drop in the end-tidal CO_2 concentration was caused by thromboembolism because heparin was given, the surgeon found no thrombi in the proximal and distal vasculature after exploring by means of a Fogarty balloon catheter, and no clots were seen while flushing the vein. The most likely explanation is air remaining behind in the subclavian vein or in the superior vena cava. Either repositioning of the arm with restoration of the circulation, or changes in cardiac output due to a painful stimulus caused by suturing of the sternum, or both, may have mobilized the air. In animal experiments it has been shown that changes in cardiac output may mobilize air (14). From studies with echocardiography it has been concluded that upward forces on the air bubble may counteract the low flow velocity in the superior cava (14). Aspiration of air through the central catheter confirmed the diagnosis of air embolism. After the second air embolism, the intrapulmonary shunt, the alveolar-arterial PO_2 difference, and the dead space ventilation sharply increased.

It was decided to continue to ventilate the patient artifically for 24 hours, because (late) pulmonary edema may occur after air embolism (15). The first postoperative chest roentgenogram suggested possible early pulmonary edema and interpleural fluid at the right side. Some days later the hazy shadow suggesting pulmonary edema had disappeared and atelectases occurred in the lower lobes of the right and the left lung. Probably this is caused by air moving to this part of the pulmonary circulation. This event may be caused by the hemodynamic outflow pattern of the right ventricle. Most thrombotic clots and most tips of flow-directed balloon-tipped catheters migrate to the right lower lobe (16). Therefore most of the embolized air probably went to the right lower lobe and, to a lesser extent, to the left lower lobe. Placing the patient in head-down position after the occurrence of the first signs of air embolism could have been another factor promoting the movement of air to these parts of the lungs.

We conclude:

1. Whenever a patient has surgery in the half-sitting position, one should be aware of the risk of air embolism. Specific monitoring, that is, capnography, should be applied.
2. Air may remain trapped in the veins of the upper half of the body; later in the operation, this air may become mobilized and reach the pulmonary circulation and result in an air embolism.
3. It may be wise to insert a central venous catheter to facilitate removal of the air in case of massive air embolism.

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Pulmonary Plasma Cell Granuloma (Inflammatory Pseudotumor) with Invasion of Thoracic Vertebra

Hi Young Hong, M.D., Melanie J. Castelli, M.D., and Jami L. Walloch, M.D.

Abstract

Plasma cell granulomas (inflammatory pseudotumors) frequently appear as localized benign tumors of the lung in patients under 30 years of age. We describe the case of a 54-year-old woman with a plasma cell granuloma originating in the left lower lobe of lung and extending into the posterior mediastinum with destruction of the T8 vertebral body and pedicle. Distinctive histologic features included granulomatous aggregation of mature plasma cells around small blood vessels and direct invasion of the posterior mediastinum with subsequent dense fibrosis and bony destruction. Immunohistochemical studies revealed polyclonal kappa- and lambda-light chains in the proliferation of plasma cells.

PLASMA cell granuloma is a benign tumor, most commonly observed in the lung of a young individual. Since Harold Brunn (1) reported a first case in 1939, many cases have been reported under the different names: xanthoma, fibroxanthoma, xanthogranuloma, histiocytoma, postinflammatory pseudotumor, xanthomatous and inflammatory pseudotumor, plasmacytoma, plasma cell tumor, sclerosing hemangioma. In 1972, Bahadori and Liebow (2) comprehensively described 40 such cases and characterized the lesion as "localized proliferations of mature plasma cells, reticuloendothelial cells and intermediate forms supported by a stroma of granulation tissue." They preferred the term "plasma cell granuloma."

This tumor usually appears as an asymptomatic, circumscribed, solitary, intraparenchymal mass in the lung. Extrapulmonary extension is a rare event. Only 10 such cases (3–10) have been reported in the English-language literature. Although it is a benign tumor, the lesion in the mediastinum can cause sclerosing mediastinitis and infiltrate to the surrounding structures.

We present the case of a middle-aged woman with a pulmonary plasma cell granuloma which directly invaded the posterior mediastinum with subsequent bony destruction of vertebral body T8.

Case Report

A 54-year-old woman sought medical help for a complaint of vague left-sided chest pain and a dry cough of 3 weeks' duration. Physical examination revealed increased bronchial breathing sounds in the left lung field. Chest roentgenogram suggested a posterior mediastinal mass. Subsequent CT scan revealed a 4 × 5 cm mass in the posterior mediastinum at the level of T7 and T8 with erosion of the vertebral body and pedicle (Fig. 1). A myelogram showed extrinsic compression of the spinal cord. Laboratory determinations were within normal limits, except for hemoglobin level decreased to 106 gm/L (normal, 120–160 gm/L), and a slightly increased platelet count of 410,000/mm^3 (normal, 150,000–400,000/mm^3).

Thoracotomy was performed and a poorly defined mass was found adjacent to the aorta grow-

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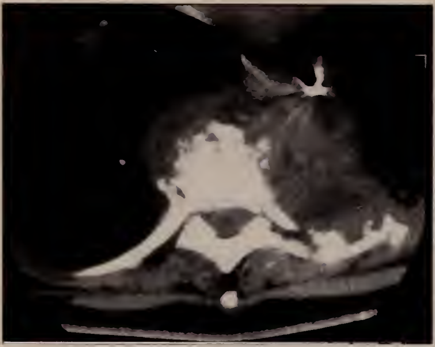

Fig. 1. CT scan. Left posterior mediastinal mass with erosion of T8 vertebral body and pedicle.

ing into the left lower lobe of lung and infiltrating into the vertebral body. Left lower lobectomy along with resection of the mediastinal mass was performed. The tumor could not be completely excised because of invasion to the vertebral body.

The mediastinal mass received in several pieces measured 5 × 5 × 3 cm in aggregate. The lesion in the lung was a 6 × 3 × 2 cm, poorly circumscribed gray-tan mass located in the posterior medial aspect of a lower lobe. Overlying pleura was not identified because of extension of the lesion.

Microscopically, the mediastinal mass was composed of dense fibrous tissue and a heavy infiltrate of mature plasma cells (Fig. 2). The plasma cells displayed a few binucleated forms. There was no mitotic activity. Russell bodies were occasionally seen. Blood vessels in the mediastinum showed medial hypertrophy and fibroblastic proliferation around the vessels, with obliteration of lumens which were delineated by elastic van Gieson, Masson's trichrome, and reticulum stains. Fibrous tissue and inflammatory cells invaded the adjacent bony structures. Periodic acid-Schiff, acid-fast Ziehl-Neelsen, and Grocott's methenamine silver stains were negative for pathogenic organisms.

The periphery of the lung lesions was ill defined, and no capsule was identified. The lesion was essentially composed of nodular aggregation of mature plasma cells around the small blood vessels (Fig. 3). The nodules were surrounded by fibroblastic spindle cells. The vessels in the center showed no evidence of fibrinoid necrosis. A mixture of inflammatory cells, predominantly mature plasma cells, was also present around the bronchioles and large blood vessels. Some bronchioles were occluded by polypoid masses of fibroblasts, plasma cells and lymphocytes. Large blood vessels showed perivascular fibrosis. The alveolar tissue between the granulomatous nodules was infiltrated with chronic inflammatory cells, predominantly mature plasma cells. In the midst of this inflammatory infiltrate were plump spindle cells with large vesicular nuclei, small nucleoli, and abundant cytoplasm (Fig. 4). Immunohistochemical studies of the paraffin-embedded tissue showed some of these cells forming vascular spaces which were well delineated with factor VIII-related antigen and vimentin. Other plump spindle cells reacted with alpha-1-antichymotrypsin and lysozyme indicating histiocytic nature. Plasma cells were positive for both kappa- and lambda-light chains.

After the diagnosis of plasma cell granuloma was rendered, further laboratory tests were done. The urine was negative for protein. The serum total protein was 71 gm/L with albumin 33 gm/L. The gamma globulin was 15 gm/L (normal, 7–17 gm/L), IgG, 19.6 gm/L (normal, 6.39–13.49 gm/L), IgA, 5.27 gm/L (normal, 0.70–3.12 gm/L), IgM, 0.90 gm/L (normal, 0.56–3.52 gm/L). The serum electrophoresis was negative for abnormal protein pattern. The erythrocyte sedimentation rate was 145 mm per hour.

The patient received adjuvant radiation therapy for a residual tumor in the spine. She developed a compression fracture of T7 and T8 vertebral bodies at the end of this course of therapy. The total dosage of 43.2 Gy was given. One month after the radiation therapy, magnetic resonance imaging (MRI) showed decreased tumor bulk in the spine; however, there was a slight involvement of the epidural space. At the present time, 8 months after surgery, she is well, although there is persistently elevated erythrocyte sedimentation rate.

Discussion

As the diversity of the terminology for the disorder suggests, plasma cell granuloma is a heterogeneous lesion that can occur in various organs of the body, including respiratory tract, mediastinum, thyroid, salivary gland, stomach, pancreas, retroperitoneum, liver, urinary tract, and central nervous system. The heterogeneous morphology of the lesion is explained by multiple cell components which comprise the lesion. Classification of the lesion depends on the cell types that predominate: plasma cell granuloma or plasma cell tumor for the lesion with predominant plasma cells, xanthoma or fibroxanthoma for one

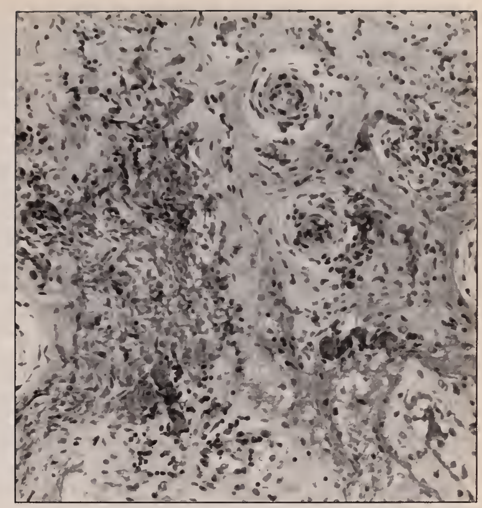

Fig. 2. Mediastinal mass. Dense collagenous tissue and inflammatory cells, predominantly mature plasma cells (hematoxylin-eosin, original magnification ×100).

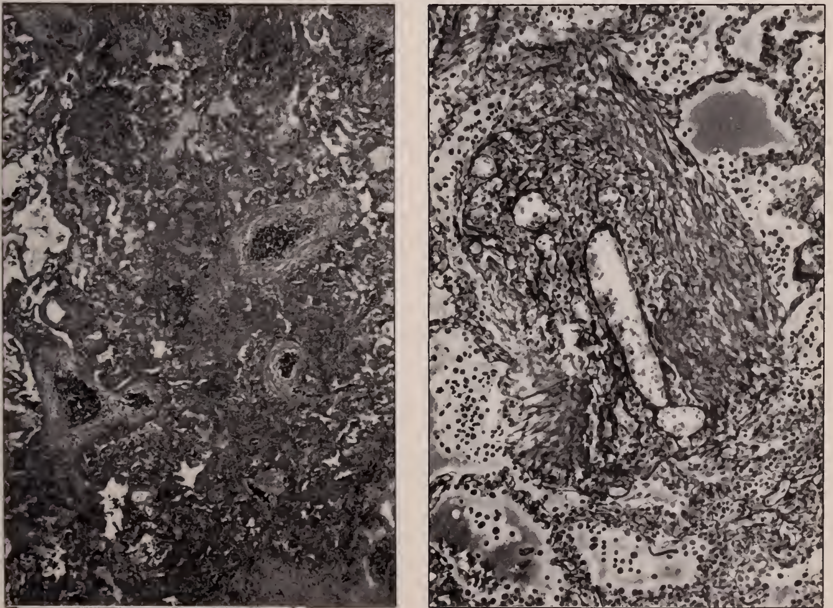

Fig. 3. Lung **Left** Nodular aggregation of inflammatory cells (hematoxylin-eosin, original magnification ×25). **Right** Nodule composed of perivascular arrangement of inflammatory cells (reticulum, original magnification ×100).

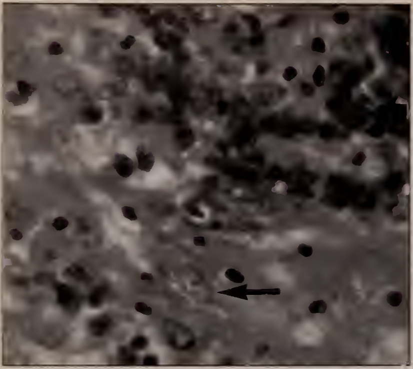

Fig. 4. Lung. Abundant mature plasma cells and a Russell body (thick arrow, top), plump spindle cells with large vesicular nuclei (thin arrow) (hematoxylin-eosin, original magnification ×400).

with predominant foamy macrophages, and sclerosing hemangioma for one with prominent vascular structures.

In 1973, Bahadori and Liebow (2) coined the term “plasma cell granuloma” and separated sclerosing hemangioma, pseudolymphoma, and plasmacytoma from plasma cell granuloma. The majority of pulmonary plasma cell granulomas occur as a solitary, well-circumscribed mass resembling a neoplasm. Its usual location is intraparenchymal, but it may occur as an intratracheal (2, 11) or endobronchial (2) mass. Extrapulmonary extension is a rare event. Among 10 reported cases in the English-language literature, 7 patients were under 15 years of age. The most common extension site was the mediastinum. In addition, there were two cases of diaphragmatic extension (4, 5) and one case of chest-wall involvement between the second and third ribs (9). No bony destruction was described in the latter case. Although the majority of reports described extensive involvement of the thoracic cavity, bony invasion, as seen in the case we report here, has not been reported. The aggressive behavior of the plasma cell granuloma in this case may raise the question of the benignity of the lesion. However, the patient did not manifest any laboratory evidence of plasmacytoma, and immunoperoxidase reactions for light chains clearly demonstrated the polyclonal nature of the plasma cells.

An interesting histologic feature in the case reported here is granulomatous aggregation of plasma cells around the small blood vessels and vascular changes seen in medium-sized and large vessels. The granulomatous arrangement was seen only in the lung lesion. Although a perivascular arrangement of plasma cells has been described (9), most of the plasma cell granulomas exhibit a close association between inflammatory cells and fibroblastic elements. Granulomatous aggregation of plasma cells surrounded by fibroblastic cells is an unusual finding. Vascular changes associated with plasma cell granuloma have been reported by a few authors. Tomita et al (12) reported a case of a sclerosing vascular variant of plasma cell granuloma, in that sclerosing vessels were a major component of the lesion. They suggested that sclerotic vascular tissue represented the end stage of the disease. Obliteration of vessels by a proliferation of fibroconnective tissue was described by Muraoka et al (9). They stated that these changes were observed at the periphery of the lesion, and not in the extrapulmonary mass. In the case reported here, both lung and mediastinal lesions showed vascular changes, although obliteration of the lumen with concentric perivascular fibrosis was more pronounced in the mediastinal mass. These vascular changes were noted in most of the lesion, suggesting that such changes might represent hemodynamic alteration rather than different evolutionary stages of the disease.

The etiology of the plasma cell granuloma is uncertain. Spencer (13) classified this lesion under the rare pulmonary neoplasm and regarded this entity as one spectrum of a process related to pulmonary histiocytoma. However, the relative stability of the lesion (2), with a few incidences of regression after a simple biopsy (8), and a polymorphic histologic pattern indicate that it may be an inflammatory process rather than a neoplasm. A history of antecedent respiratory infection has been described by several authors (14, 15). Viral etiology was the most often suggested underlying cause. However, other infectious agents may play a role (16). Tissue culture studies (17) and polyclonality of plasma cells (9, 18) further support the reactive nature of the plasma cell granuloma.

This granuloma is a benign lesion sometimes associated with nonspecific symptoms such as cough, hemoptysis, clubbing of fingers, and cyanosis. Abnormal laboratory findings include elevated ESR, thrombocytosis, and hypergammaglobulinemia. Most of the plasma cell granulomas are stable or slow growing, although rare cases of rapid growth (19) or regression (8) have been reported.

Complete surgical resection is the treatment of choice. In surgically unresectable cases, radiation therapy showed good response (6, 10). Recurrence rate is almost nil if the lesion is completely removed. Imperato et al (10) reported one case of recurrence four years after complete surgical removal.

Mortality is extremely low and it is usually associated with operative complications. Among 10 cases of extrapulmonary extension, only one patient died, as a result of sclerosing mediastinitis (2). In spite of the benign nature of the lesion, vascular invasion has been reported by Warter et al (16). Among 6 patients with vascular invasion, one patient died of pulmonary vein invasion. The case we report on here showed features of sclerosing mediastinitis with infiltrating components derived from both cellular and collagenous elements. The patient partially responded to radiation therapy; however, the follow-up period is not long enough to evaluate the effect of therapy.

In conclusion, plasma cell granuloma is a benign lesion of unknown etiology. Although extrapulmonary extension may indicate aggressive behavior, response to radiation therapy is excellent in general.

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Pelvic Mass as the Initial Symptom of Ovarian Leiomyoma

Ilana Cass, Debra S. Heller, M.D., Martin Goldstein, M.D., Woo Sung Ahn, M.D., Ira S. Schwartz, M.D.

OVARIAN leiomyoma is a rare mesenchymal tumor, accounting for only 1% of benign ovarian neoplasms (1). Fewer than 50 cases have been described in the literature (2). The paucity of published reports may be due in part to the difficulty in clearly distinguishing ovarian leiomyoma from the more common fibrothecoma. We describe the case of a patient with leiomyoma of the ovary whose initial symptom was an adnexal mass and discuss the clinical and pathologic features that distinguish this leiomyoma from fibrothecoma.

Case Report

A 38-year-old woman with a previously unremarkable gynecologic history was found on routine examination to have a 6.0 cm × 5.0 cm right adnexal mass. Ultrasound confirmed a solid homogeneous mass. Serum level of the antigen Ca-125 was less than 5 units/mL. The patient underwent exploratory laparotomy, with removal of a right ovarian mass, and uterine myomectomy.

Three uterine leiomyomata, measuring up to 4.0 cm in greatest dimension, were identified. The solid ovarian neoplasm measured 5.5 × 5.0 × 4.5 cm and was well circumscribed. It was completely surrounded by ovarian tissue (Fig. 1). Histologically, the tumor was composed of interlacing bundles of spindle cells with blunt-ended ovoid nuclei, identical in appearance to the uterine leiomyomata (Fig. 2). Immunohistochemical staining for desmin, a muscle cell intermediate filament, was strongly positive (Fig. 3).

Discussion

Sangalli first described ovarian leiomyoma in 1862, followed by the observation, in 1888, that fibrothecoma and leiomyoma were two distinct entities (3). A few reports of ovarian leiomyoma associated with pregnancy subsequently appeared in the literature (4). The first nongestational leiomyoma was not reported until 1953 (5). Fallahzadeh et al (3) present a good review of the literature.

Ovarian leiomyoma is characterized by smooth muscle cell proliferation and is completely surrounded by ovarian cortex. It usually measures 3 cm or less in greatest diameter and may range in color from reddish to gray. Histologically, the tumor has a whorled appearance, composed of coarse interlacing fascicles of smooth muscle cells. Degenerative changes similar to those characteristic of uterine leiomyoma, such as hyalinization, hemorrhage, calcification, and cyst formation, may be seen (3). All of the reported cases have been unilateral (6). There is no evidence of intrinsic hormonal activity, although this neoplasm appears to be stimulated by estrogen, as is its uterine counterpart, with which it is often associated. The majority of ovarian leiomyomas have not been responsible for significant local symptoms or menstrual irregularities (6).

The reported age range for this infrequent tumor is 20–65 years; 51 years was the mean age in Fallahzadeh's series (3) and 42 years the mean in Matamala's cases (2). However, a number of cases have occurred in women of childbearing age, both nulliparous and multiparous, and several cases manifesting during pregnancy have been reported (4).

In contrast, the more commonly encountered fibrothecoma is described as locally symptomatic and not infrequently is associated with menstru-

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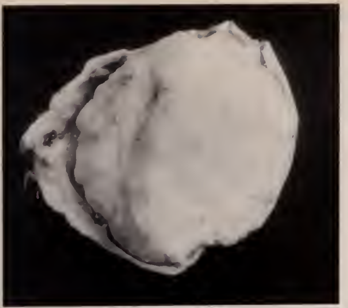


Fig. 1. Gross appearance of ovarian leiomyoma, completely surrounded by compressed ovarian tissue.

al abnormalities related to estrogenic secretion. Fibrothecoma tends to be uniformly whitish-yellow and firmer than myoma (6).

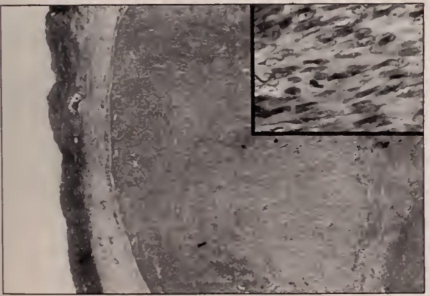
In addition to its rarity, a number of factors may explain the lack of reports of ovarian leiomyoma. First, it is usually an incidental finding, generally measuring less than 3 cm and being asymptomatic. Second, the similar appearances on gross examination of myoma and fibrothecoma may result in misdiagnosis (2). Additionally, the predominant cell type in an ovarian mass may be difficult to discern microscopically because of secondary fibrous changes or a mixed composition of fibrous matrix and musculature (6).

Immunohistochemical and electron microscopy studies are valuable in differentiating fibrothecoma from myoma. The smooth muscle cells of leiomyoma show specific desmin-positive intermediate filaments. Ultrastructurally, leiomyoma exhibits the characteristic features of smooth muscle: dense bodies, pinocytotic vesicles, and basement membrane (7). Fibrothecoma may show lipid and ultrastructural features consistent with steroid hormone secretory cells, and it lacks the smooth muscle cell characteristics of leiomyoma.

In order to rule out a parasitic leiomyoma arising originally from the uterus which has attached to an ovary, the tumor must be completely surrounded by ovarian tissue. Further, primary ovarian leiomyoma must be distinguished from leiomyomatosis peritonealis disseminata, which secondarily involves the ovary and occurs on the ovarian surface (2).

Various theories have been offered to explain the origin of ovarian leiomyoma. In the normal ovary, smooth muscle cells are found in numerous locations, all of which have been proposed as possible sites of origin. Wallart (8) proposes the mesovarium, describing in it the existence of two layers of smooth muscle, one subserosal and the other intervascular. Both layers extend to the ovarian hilus and medulla without reaching the cortex, which principally contains fibroblasts. Wallart contends that the number of smooth muscle cells is greatest during the fertile period of life and that marked hypertrophy and hyperplasia of this musculature are seen during pregnancy. He indicates, therefore, that the myoma originates in the medulla and hilus, whereas the fibroma originates in the cortex.

Henrotin and Herzog (9) claim that the tumor is derived from the vascular musculature



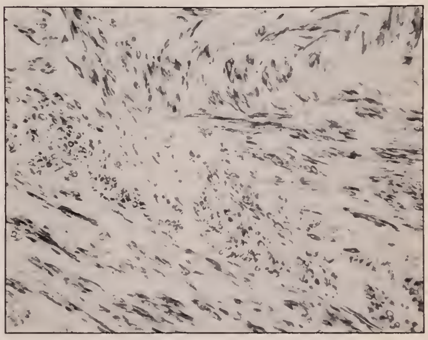


Fig. 2. **Left** Section of tumor surrounded by ovarian tissue (H&E, original magnification ×40). The tumor is composed of interlacing bundles of smooth muscle cells (inset, H&E, original magnification ×400).

Fig. 3. **Right** Positive staining of tumor cells for desmin (ABC immunohistochemical method, original magnification ×220).

of the ovary. In support of this theory, Fallahzadeh (3) points out that the cortical vessels are smaller, often hyalinized, and generally contain less smooth muscle than the numerous thick-walled vessels in the hilus. However, Wellmann (6) discusses the difficulty he encountered identifying the origin of the branched and interconnected smooth muscle cells seen coursing between tumor and vessel wall in his study of ovarian leiomyomas. He suggests that primitive ovarian stromal cells may differentiate to smooth muscle, with ultimate tumor formation under hormonal influences, that is, the overproduction of estrogen. Vestigial remnants of the Wolffian body also contain smooth muscle and may serve as a site of origin of ovarian leiomyomas (6). There has been little evidence of a leiomyoma developing from a previous focus of endometriosis in the ovary (3). Presumably this phenomenon is explained by the rare occurrence of smooth muscle fibers in the islands of endometriosis (6).

The majority of reported ovarian leiomyomas, including the case we report here, have been coincident with uterine myomas, and the question of a common hormonal stimulus has been raised (3). The case we report is unusual in that the lesion was larger than most previously described tumors and its initial symptom was an adnexal mass.

In summary, ovarian leiomyoma is an uncommon benign mesenchymal neoplasm that is usually an incidental finding. We have described one such tumor which was larger than average and appeared as a pelvic mass. We have discussed the features that distinguish this neoplasm from the more frequently encountered fibrothecoma of the ovary, especially the utility of immunohistochemical and ultrastructure studies to confirm the smooth muscle nature of the neoplasm.

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THE MOUNT SINAI JOURNAL OF MEDICINE

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Award winners are Class of 1990 except as noted.

The Mount Sinai Journal of Medicine Awards 1989

Ralph Colp Prize

The 1989 Ralph Colp Prize for the best surgical paper published in *The Mount Sinai Journal* during the calendar year went to E. Converse Peirce II, MD, and Harry Schanzer, MD, for their article "Arterial Flow in Venous Volume Studies" (vol. 56, no. 1). Both authors are with the Department of Surgery at the Mount Sinai School of Medicine (CUNY); Dr. Peirce is Professor of Hyperbaric Medicine there, and Dr. Schanzer is Professor of Surgery and Director of Surgical Research. The award was established by colleagues and friends of Ralph Colp, distinguished surgeon and for many years chief of surgery of The Mount Sinai Hospital.

Globus Award

The 1989 Globus Prize for the best paper with a clinical orientation published in this journal during the calendar year went to Joel M. Zinberg, MD, JD, for his paper "AIDS: The Duty to Treat" (vol. 56, no. 3). Dr. Zinberg is Julius Silver Fellow at Columbia University School of Law, holds posts at The Center for the Study of Society and Medicine and Columbia University College of Physicians and Surgeons, and is assistant attending surgeon, Mount Sinai Hospital, and assistant clinical professor, Mount Sinai School of Medicine (CUNY). This award honors Joseph H. Globus, founder and first editor-in-chief (1934–1952) of *The Mount Sinai Journal.*

Student Prize

The 1989 Student Prize for the best student paper published in this journal has been awarded to John R. Wagner, MD, for "Aortic Graft-Enteric Fistula and Paraprosthetic-Enteric Fistula: A Review" (vol. 56, no. 2), written when the author was a third-year student at the Mount Sinai School of Medicine (CUNY). Dr. Wagner is currently an obstetrics-gynecology resident at University Hospital, State University of New York, Stony Brook, LI.

Grand Rounds

Allen Arieff has been involved for many years in research on problems of water balance and has written extensively on this subject. He has also edited a superb textbook on fluid electrolyte and acid base disorders. He has been a major voice of reason in the enormously controversial area of the pathophysiology and approach to hyponatremia. This Grand Rounds was when it was presented orally, and is here in its printed form, exceptionally interesting and illuminating. It is a demonstration of how careful clinical observations brought into the laboratory can lead to enormous insight into the pathophysiology of an important clinical syndrome.—Richard Stein

Hyponatremia

ALLEN I. ARIEFF, M.D.

HYPONATREMIA—which I define as a plasma sodium concentration less than 130 mmol/L—strikes about 2% to 3% of all hospital patients. It is encountered by cardiologists, endocrinologists, nephrologists, general surgeons, and perhaps others. Yet I think it is one of the least understood disorders. Everybody thinks they know everything about it and perhaps that's why it's misunderstood.

Although hyponatremia has a number of causes, some are so common they overwhelm the others. Most patients in the hospital with hyponatremia don't have anything complicated at all. They have heart failure, cirrhosis of the liver, or nephrotic syndrome. Outpatients develop hyponatremia, as sometimes happens from the use or abuse of diuretics. Many instances of hyponatremia have been labelled the syndrome of inappropriate secretion of antidiuretic hormone. But in fact we now know that no matter what the cause of hyponatremia—with one exception—everybody with it has a high level of antidiuretic hormone. The only exception I know of is acute water intoxication. And I group the postoperative state as a separate cause because, although postoperative patients have high levels of antidiuretic hormone that have often been called inappropriate, some very good evidence has now come from the United Kingdom that everyone who has surgery for any reason has a severe functional deficiency of circulating blood volume after the operation. Thus the high levels of antidiuretic hormone may not be "inappropriate" at all, so I group that separately.

Some causes of hyponatremia are exotic and esoteric. Addison's disease was once one of these exotic causes—I used to tell house officers and medical students that we never saw hyponatremia from Addison's disease anymore because Addison's disease is now very rare. But AIDS is now a common entity, especially in New York and San Francisco, and human immunodeficiency virus can directly invade the adrenal gland and lead to necrosis. So we now get something that I have to call Addison's disease in patients with AIDS. The salt-wasting syndromes, pseudohypoaldosteronism, cerebral salt-wasting syndromes, polydipsia, and febrile illness in older women are interesting, but uncommon. They don't relate to the substance of this talk: why one has to worry about hyponatremia, what it does

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Adapted from the author's Grand Rounds in Medicine presentation at Mount Sinai Medical Center, June 23, 1989. From the Department of Medicine at the University of California in San Francisco and the Geriatrics Division, Veterans Affairs Medical Center, San Francisco, CA. Address reprint requests to Allen I. Arieff, M.D., Chief, Geriatrics Research (111G), Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, CA 94121.

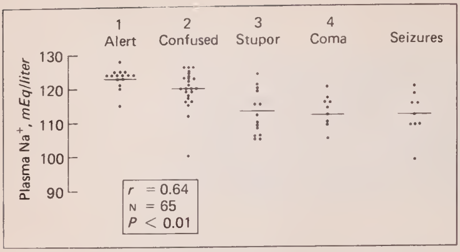


Fig. 1. **Left** Plasma sodium levels plotted against clinical status of all comers—male, female, young, old, postoperative, those taking diuretics, and those with other causes for hyponatremia—with sodium levels under 128 mEq/L (128 mmol/L). Sodium level is not the sole determinant of clinical status. Horizontal bar in each column indicates average. Reprinted with permission from Arieff AI, Llach F, Massry SG: Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes, Medicine (Baltimore) 1976; 55:121–129 (ref. 11).

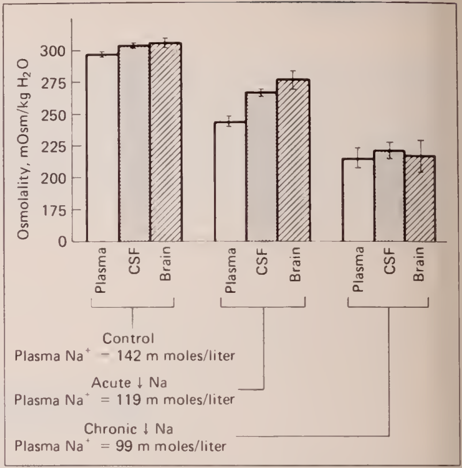


Fig. 2. **Right** Osmolality in rabbit plasma, central spinal fluid (CSF), and brain in three groups of rabbits: control, group undergoing rapid but moderate sodium level reduction (Acute ↓ Na), and group undergoing slower but greater sodium level reduction (Chronic ↓ Na). SE (I) is shown at top of each bar. Data extracted from ref. 11.

that's bad, and—perhaps more important—what can actually be done about it.

Why Hyponatremia Is Worrisome

Hyponatremia is probably in itself an important cause of permanent brain damage. It is often believed to be a comorbid factor, but I'm going to try to show here that it is in itself dangerous. A literature review by Anderson (1) shows that in patients with either heart failure, tuberculosis, diarrhea of childhood, or acute myocardial infarction, mortality in those who do not have hyponatremia is only about one seventh that in patients who do have it. To be dramatic, hyponatremia accompanying a number of common disorders, including cirrhosis of the liver, involves a 700% increase in mortality. Thus as a comorbid factor, hyponatremia, even when defined only as a sodium level below 130 mmol/L, is important. Surprisingly, the recent literature (as of 1986) shows that a sodium level below 120 mmol/L, when accompanied by central nervous system symptoms, has an overall mortality of almost 40%; among those who are also alcoholics it's almost 70%. So hyponatremia alone, when the sodium level is below 120 mmol/L, entails tremendous mortality.

But I think one of the keys to mortality is the presence or absence of symptoms. If a person has a sodium level of 120 mmol/L and is asymptomatic, the mortality is close to zero. If the patient has nothing more than headache, nausea, and vomiting, mortality is about 40%. I must emphasize that the most important factor in determining both morbidity and mortality from hyponatremia is the presence of symptoms.

I think many of the recent arguments in the literature relate to how people define hyponatremia. A 70-year-old man taking diuretics who has a sodium level of 110 mmol/L and a 28-year-old woman who has recently had surgery and also has a sodium level of 110 mmol/L are totally different in regard to prognosis, pathophysiology, and other variables. Nonetheless, there are some exceptions; looking at the literature on mortality of a sodium level below 106 mmol/L, all comers, yields a mortality risk of about 2 out of 3 (67%), increased in alcoholics to about 90%. I must point out here something I reiterate in my concluding remarks: if patients don't have alcoholism and are treated with hypertonic saline by any means, the mortality is essentially halved. So therapy definitely plays a role in moderating the mortality from this disorder. But huge mortality does result from a sodium level below 106 mmol/L, regardless of differences in age, sex, height, weight, and general susceptibility.

If the sodium gets low enough, the body's defenses can easily be overcome. A study I did with colleagues when I was a fellow at UCLA a number of years ago raised a lot of questions (Fig. 1). I think we're on our way to answering some of them. In all patients who had a sodium level of 128 mmol/L or less, we correlated the level of serum sodium with initial state of consciousness and with presence or absence of grand mal seizures—including all comers, male, female, young, old, postoperative, those taking diuretics, and those with other causes for hyponatremia. The results can be viewed two ways. Just looking at the numbers suggests a significant correlation. But the overlap is enormous: a person who's alert can have a sodium level of 112 mmol/L, and a person in frank coma can have a sodium level of 120 mmol/L. So for useful classification the numbers don't really hold up very well. Something else is going on.

When I was a medical student, we were taught that morbidity in hyponatremia related to two factors: how low the sodium went and how rapidly it got down that low. Although there is a certain amount of truth to that rule, what I'm going to describe here may dispel reliance on it as absolute. How low the sodium is and how rapidly it went down is not in fact all-important, because in certain individuals, sodium levels all the way from normal to 100 mmol/L cause no problems at all, whereas in other individuals, levels from 140 to 128 mmol/L may prove rapidly fatal.

Brain Responses: Gain in Water, or Lower Osmolality. To review some of the important factors, I focus for a moment on some data in laboratory animals. If the plasma osmolality were to be lowered abruptly from 300 mmol/L down to 200 mmol/L, the brain has really only two responses:

It can gain water, and when it gains water it will expand. Because of the rigid confines of the skull, the brain can expand only by about 6% of its normal volume. When that happens something has to give, or something has to go someplace else, producing brain damage.

Instead of expanding, the brain can lower its osmolality, from 300 mmol/L down to say 200 mmol/L. And the only way it can do this is by extruding the cations sodium and potassium by some active pathway. If that were to happen, the brain could lower its osmolality without gaining much water.

A composite of these two responses—a little bit of both—may occur; that is, the brain can lower its osmolality, with some loss of cation and a gain of water. These are active pathways, and the reason I emphasize extrusion of cations is that the internal concentration of sodium plus potassium is about 150 mmol/kg cell H_2O. Since in humans the osmolality of the brain is less than 300 mOsm, there really isn't much else that can be osmotically important. So it really has to center on those two cations plus their anions.

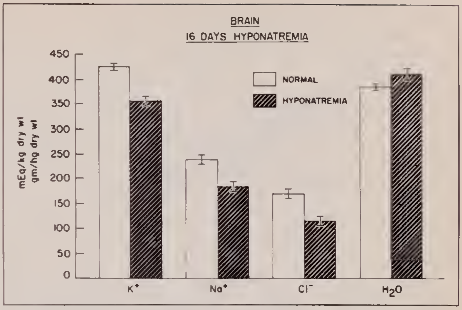


Fig. 3. Comparison of "normal" (white bars) and "hyponatremia" (hatched bars) levels in brain of potassium (K^+), sodium (Na^+), chloride (Cl^-), and water (H_2O) in animals after 16 days of hyponatremia. Animals remained asymptomatic. SE (I) is shown at top of each bar. Reprinted with permission from ref. 11.

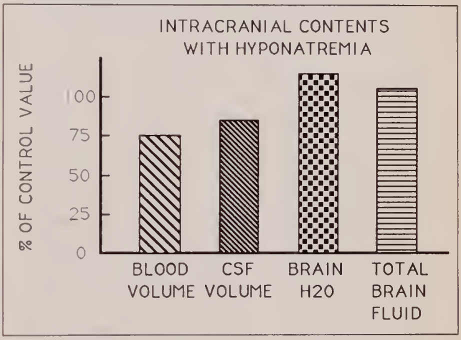


Fig. 4. Intracranial contents after hyponatremia was induced in rabbits. Data extracted from Stern EW, Coxon RV: Osmolality of brain tissue and its relation to brain bulk, Am J Physiol 1964; 204:1–7 (ref. 3).

Some examples of what actually does happen to brain, plasma, and spinal fluid osmolalities in rabbits are shown in Fig. 2. Normally the osmolalities are about 300 mOsm/kg, and the three compartments are identical. Rapidly lowering the sodium level from about 140 mmol/L to only 120 mmol/L promotes an osmotic gradient from plasma to brain of more than 25 mOsm, which would encourage the movement of water into the brain. In fact, lowering the sodium by this relatively modest amount rapidly—within one day—produces 100% mortality. There is no survival, and on autopsy these animals will have cerebral herniation. So a relatively modest lowering of plasma sodium leads to 100% mortality; but when the level is lowered even more, from 140 mmol/L to 100 mmol/L, but over a longer period of about a week, the osmolality of the three compartments remains the same, and the mortality is much less (about 25%).

Thus the brain can undergo adaptations, and

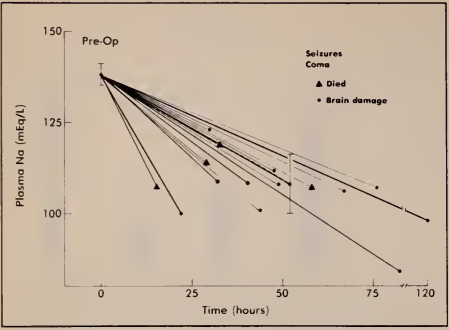


Fig. 5. Postoperative course of 15 women showing change in plasma sodium (Na) levels plotted against time. All 15 developed seizures and coma and either sustained permanent brain damage or died. Average period after surgery of brain damage and of death is shown in broken dark line. Data extracted from Arieff AI: Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women, N Engl J Med 1986; 314:1529–1535 (ref. 5).

they do not depend just on osmotic gradients. In the entire literature on animal work in this area, acute hyponatremia of less than 4 hours duration, in combined studies of cats, rats, mice, and rabbits, when serum sodium is abruptly lowered to 110 mmol/L from normal in 4 hours or less, the brain has gained a lot of water, increasing its volume by approximately 12%, and has lost a lot of sodium and potassium attempting to compensate. So of the two mechanisms I suggest the brain can undergo, it does a little of both. But this is not good enough, because all of these animals die when serum sodium is lowered from normal to about 120 mmol/L in less than 4 hours. I mentioned above that when the brain expands by about 6% of its volume there is a risk of herniating. When it expands by 12%, it is not able to resist herniation.

Animals who have had low sodium levels for a couple of weeks tell a different story (Fig. 3). The lowering of brain content of potassium-sodium-chloride is such that the fall in osmotically active cation is the same as the fall in brain osmolality, and the animals survive. There is still a small increase in brain water, but it is less than 6%, so there is no herniation. The animals are still asymptomatic, I think because of the small amount of brain edema. This is one of the keys to predicting brain damage from hyponatremia—the presence of symptoms. Verbalis has recently shown (2) that if one lowers the sodium level from normal to about 110 mmol/L over a period of about 10 days, maintains the animals in that state for about a month, and keeps up their nutrition, they can survive for about a month. So chronic asymptomatic hyponatremia, even with sodium levels as low as about 110 mmol/L, is not incompatible with survival, at least for a couple of weeks.

In addition to the changes in the electrolytes, an important factor in what causes brain damage is cerebral hypoxia. Stern and associates (3) gathered data about 25 years ago in laboratory animals (Fig. 4). When these researchers produced acute hyponatremia in rabbits, the brain blood volume was reduced by over 25%, the cerebral spinal fluid volume was also reduced, the brain water increased, and the brain total fluid was held relatively normal. So the brain has remarkable homeostatic mechanisms, but to keep from herniating, it gets rid of spinal fluid volume and blood. These observations have recently been confirmed (4). Despite the homeostatic mechanisms, the brain cannot sustain much lowering of its blood flow. With the brain edema and the herniation and the lowering of cerebral blood volume, you get cerebral hypoxia. This is one of the major factors leading to brain damage from hyponatremia.

Male-Female Difference. But I think one of the most important factors in Verbalis' study (2)

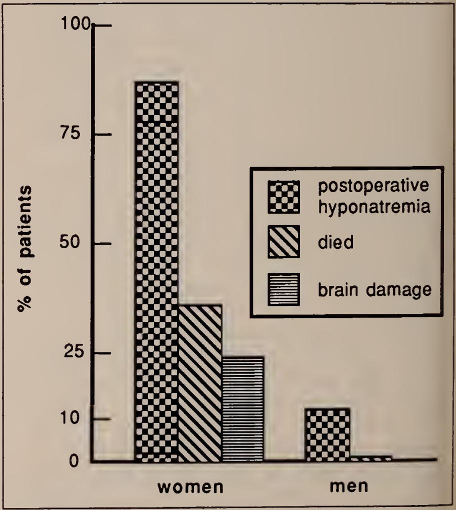


Fig. 6. Patients reported in the literature up to beginning of 1988 as developing hyponatremia postoperatively. Of the total of 75, all reported to be healthy preoperatively, roughly 90% were women, primarily women of childbearing age. Data extracted from Arieff AI: Osmoregulatory failure: physiology and strategies for treatment, Hospital Practice 1988; 23:173–194 (ref. 6).

is that all the animals he studied were males; the same is true of several other studies. The mortality and morbidity from hyponatremia is almost exclusively a disorder of young females. It virtually does not occur in males. This is a fairly recent observation.

During a 10-year period I was able to consult on 15 women who had had surgery and were experiencing a stormy postoperative course (5). They had been in good health and their sodium levels were normal before they were operated on. Over an average period of two days after surgery, in a range varying from about 9 hours to about 5 days, their sodium levels fell from about 140 to 108 mmol/L. Every one of them developed seizures and coma, and they all died or suffered permanent brain damage. It wasn't until I was finally putting this data together for publication (it was published in 1986) that I realized all the patients were women (Fig. 5).

In a literature search I reviewed all the patients I could find as of the beginning of 1988 who had postoperative hyponatremia and who had, from the literature at least, no other serious underlying disorder (Fig. 6) (6). I picked patients with postoperative hyponatremia to study because in general they are largely healthy, have been studied before the hyponatremia, and can be screened to exclude patients with other disorders. The patients had elective surgery—for uterine fibroids, cosmetic surgery, setting of fractures. About 90% of these patients turned out to be women, young women whose average age was about 34. And virtually all the mortality and all the morbidity occurred in the women. In the men, mortality and morbidity were distinctly unusual.

Thus a simple literature search revealed that in otherwise healthy patients, virtually all the brain damage is in women, usually young women. Finally, something that might show why vehement arguments arise over hyponatremia, over how to treat it and how not to treat it, over whether it's bad or not so bad. (It is not always bad.)

One can construct a prototype of what happens postoperatively in patients who get the syndrome (Fig. 7). They have normal serum sodium levels, they have elective surgery, they wake up from anesthesia, but during this time they get headache, nausea, and vomiting. On the average, two days after surgery the typical patient is sitting in her room, alert, talking with someone else in the room. And then, over a period of 20 minutes or less, she goes from being alert and talking, to seizures, respiratory arrest, and coma. And every one either dies or suffers permanent brain damage. This prototype has been well defined because since first describing it with my colleague J. C. Ayus from Baylor Medical Center (7–9), we have seen over 150 additional cases in about a year and a half.

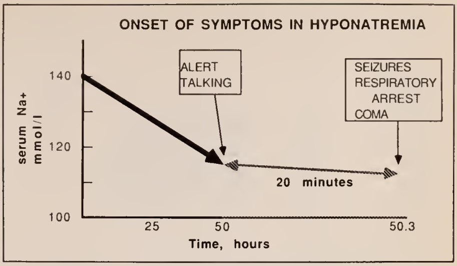


Fig. 7. Pattern in those postoperative patients—typically young women—who develop symptoms of hyponatremia, most commonly headache, nausea, and vomiting. Prevention of hyponatremia in such women is imperative, because most of those who develop symptoms suffer brain damage or die. Data extracted from Ayus JC, Krothapalli R, Arieff AI: Treatment of symptomatic hyponatremia and relationship to brain damage: a prospective study, N Engl J Med 1987; 317:1190–1195 (ref. 7).

I must stress that in almost every one of these patients, the cause of death is not correctly stated on the discharge summary. They are said to have had myocardial infarctions, strokes, encephalitis, or arrythmias, none of which turn up in any laboratory evidence or in the autopsy.

Wrong Differential Diagnosis. This sort of symptomatology coming on so suddenly and so unexpectedly has inspired an enormous differential diagnosis. Most of the patients had what appeared to be decorticate posturing or opisthotonos, or both, which were felt to be extrapyramidal responses to prochlorperazine or promethazine, but really were due to decorticate posturing. Even if the patients had not received compazine or phenergan, they were still said to have extrapyramidal reactions. Often, because they had had surgery and received ordinary doses of morphine or meperidine, they were said to have respiratory arrest due to narcotics. The doses were really rather small, and no patient responded to narcotic antagonists. They're often said to have primary aspiration pneumonia, but in fact the aspiration always could be shown to have occurred after the respiratory arrest, not before. A ruptured cerebral aneurysm always entered the diagnosis, leading to computed-tomography scans, magnetic resonance scans, and cerebral angiograms in most patients. No aneurysms were ever found.

The worst misreading was a presumptive diagnosis of encephalitis in three patients I was asked to see. These patients had been subjected to exploratory craniotomy for suspected herpes encephalitis, even though the serum sodium levels were noted to be below 105 mmol/L on the chart. As I mentioned, none of these differential diagnoses was ever confirmed.

Why in Women and Not in Men? To determine why the syndrome essentially occurs in women we undertook some studies on additional groups of men and women and laboratory animals. At Baylor, J. C. Ayus and I studied ten relatively healthy men who underwent elective transurethral prostate surgery in the usual manner with distilled water and glycine irrigation of the bladder (9). Just to show that a lot of what you learn in medical school isn't always true, their preoperative sodium levels, which were about 140 mmol/L, decreased in just 4½ hours to about 100 mmol/L. They all had headache, nausea, and vomiting. Hyponatremia was diagnosed. None developed respiratory arrest. Defying all rules of therapy by those who insist on slow treatment as the remedy, their serum sodium was raised with intravenous 5% sodium chloride from about 100 mmol/L to about 125 mmol/L in about 4½ hours. All of them did very well. We are not recommending this rate of treatment; nevertheless, no sequelae were seen.

At that time we had seen another 34 women, all of whom underwent elective surgery, such as breast reconstruction, plastic surgery of the face, hysterectomy, or setting of imperfectly aligned fractures (9, 10). All were judged normal on preoperative cardiograms, chest x-rays, urinalysis, various blood chemistry studies, and physical examination. The average age was 34 years, but some were as young as 18.

What happened to them is quite different from what happened to the men. Postoperatively their serum sodium levels went from normal to only about 117 mmol/L in about a day and a half. They developed nausea, headache, and vomiting, but when they developed seizures, respiratory arrest, and coma, their serum sodium levels were higher than those of the men we studied. All either died or suffered severe, permanent brain damage. So lowering the sodium levels much less and over a much longer interval was more devastating in women, establishing that a definite difference existed in the responses of men and women.

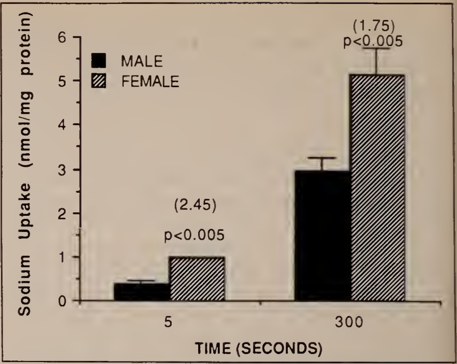


Fig. 8. Veratridine-sensitive component of sodium uptake in hyponatremic rats. ⊤ atop each bar indicates SE. Numbers in parentheses are female:male ratios. Data extracted from Fraser CL, Kucharczyk J, Arieff AI, Rollin C, Sarnacki P, Norman D: Sex differences result in increased morbidity from hyponatremia in female rats, Am J Physiol 1989; 256 (Regul, Integ & Compar Physiol 25):R880–885 (ref. 18).

Seeking to throw a little light on the possible cause of this difference, we did our first simple studies in laboratory animals. In a group of rabbits we lowered the sodium level to a mean of 104 mmol/L by nasogastric water and subcutaneous vasopressin over a couple of days. This serum sodium level was maintained for 5 days (11). The mortality in the males was about 20%; in the females, about 85% (11).

In subsequent studies of similar groups of animals before they died, we found that in the

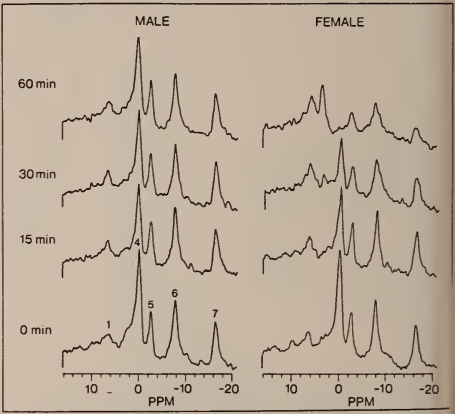
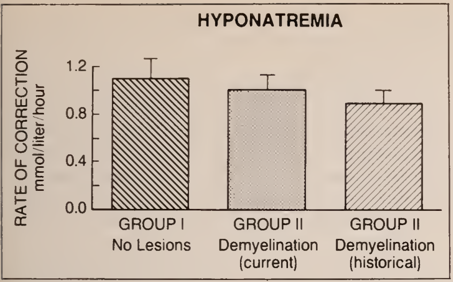


Fig. 9. Magnetic resonance spectroscopy showing male-female differences in adenosine triphosphate (ATP) synthesis after intraperitoneal dose of vasopressin was administered to rats without hyponatremia. ATP peaks alpha (5), beta (6), and gamma (7) and phosphocreatine (4) and inorganic phosphorus (1) peaks are shown. In females, ATP synthesis is almost completely destroyed; in males, no change is undergone. Reprinted with permission from Fraser CL, Kucharczyk J, Arieff AI, Rollin C, Sarnacki P, Norman D: Sex differences result in increased morbidity from hyponatremia in female rats, Am J Physiol 1989; 256 (Regul, Integ & Compar Physiol 25):R880–885 (ref. 18).



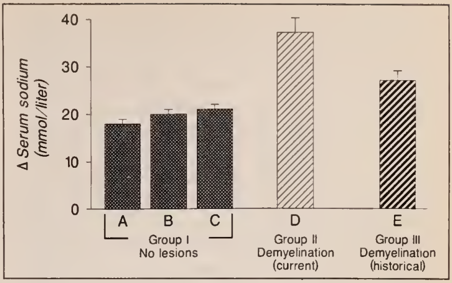


Fig. 10. Left Rate of correction of hyponatremia in prospective study participants with and without demyelinating lesions and in patients in historical literature survey with demyelinating lesions. All three groups had a similar rate: about 1 mmol/L per hour. ⊤ atop each bar indicates SE. Data extracted from Ayus JC, Krothapalli R, Arieff AI: Treatment of symptomatic hyponatremia and relationship to brain damage: a prospective study, N Engl J Med 1987; 317:1190–1195 (ref. 7).

Fig. 11. Right Absolute change in serum sodium level in same three groups. Change per day in group 1 was less than 20 mmol/L, in group 2 close to 40 mmol/L, and in group 3 close to 30 mmol/L. ⊤ atop each bar indicates SE. Reprinted with permission from ref. 7.

control state, the brain water in male and female rabbits was exactly the same. In the hyponatremic state, brain water remained about the same in the males, but in the females it increased by a substantial amount, far more than 6%. So one of the reasons the females died more often is that they had more brain edema (9). Why? Again at the basic level, we looked at the brain tissue cations, the sodium and potassium, the major osmotically active substances in the brain. We found that in male hyponatremic rabbits, the brain sodium level is below normal, whereas in the female it's just about normal. That represents a substantial and highly significant difference. The brain potassium level in the males was found to be below normal, but about normal in the females. In general, then, the female rabbits die more readily because their brains swell more for the same degree of hyponatremia in the same period of time. They swell more because they have a higher internal osmolality, because they have more sodium and potassium.

The Biochemical Reason. The mechanism is not brought out by this study, but there is a good biochemical reason for the increased morbidity and mortality in females. In our data, the men had a greater and more rapid fall in sodium, 37 vs 24 mmol/L, and in much less time—4½ hours vs more than 36 hours. The men had some morbidity, but no mortality. The women had 100% percent morbidity and some mortality. So just how much and at what rate the serum sodium decreases does not determine who is going to suffer brain damage. And in rabbits with a sodium level of 104 mmol/L, males have much less mortality than females because they can better extrude osmotically active cation from the brain, and thereby lower cellular osmolality and avoid brain edema.

Thus a clearcut difference in outcome is related to sex, probably due to some hormonal or biochemical differences. That's where we are at the present time. This was really done about a year ago, and the animal work has only been presented at the American Society of Nephrology (9), not actually published yet.

The Relationship between Hyponatremia and Encephalopathy at the Bedside

Putting all this together, I think the relationship between hyponatremia and encephalopathy at the bedside can now be understood. In retrospect it is actually rather simple. With hyponatremia there is, as one would expect, some water movement into the brain. The brain swells. The only consistent symptoms of brain edema are headache, nausea, and vomiting. Most of the time nothing happens.

Vasopressin levels are high in every patient after an operation. This may cause movement of water into the brain even without hyponatremia. So a lot of the reason for headache, nausea, and vomiting after surgery may be subclinical brain edema. If this edema is not relieved, if the serum sodium level keeps falling, the patient may get beginning tentorial herniation. Some of the clinical manifestations are urinary and sometimes fecal incontinence; decerebrate posturing; dilation of first one pupil, then of both, and fixation of both pupils; bradycardia; hypertension; and seizures. This is well described in the neurosurgery literature under increased intracranial pressure (12–15), but does not seem to find its way into the literature of internal medicine at all.

Tentorial herniation does occur abruptly, and in our experience coma can occur over about a 20-minute period from the time the patient was last noted to be alert (Fig. 7). Up until then, the brain has compensated very well. Once tentorial herniation occurs, the patient has respiratory arrest with one or both pupils fixed and dilated. These patients are often declared brain dead right afterward—a major clinical error, because the reason they have fixed dilated pupils is not that they have brain death, but because they have traction on the third nerve from the herniation (15). So they are not brain dead, but they do have fixed, dilated pupils.

Now we can better understand the cause of brain damage if a patient has had hyponatremia. Certainly respiratory arrest with an already compromised brain blood flow cannot be good. It leads to cerebral hypoxia. Microscopically a lot of the brain damage is due to brain swelling and increased intracranial pressure. Cerebral herniation causes occlusion of branches of the middle and cerebral artery and can cause traction on the third nerve, avulsion of the pituitary gland, and infarcts of the medulla. Somehow it's crept into the literature that intravenous sodium chloride, which is often used to treat this progression, can cause brain damage (16, 17). This makes no sense at all, as I show below.

A set of studies at the single-cell level reveals why the morbidity and mortality occur in females rather than males. With C. L. Fraser, P. Sarnaki, and other colleagues, I looked at transport of sodium and potassium in synaptosomes, which are analogous to isolated brain cells, from male and female rats. We looked particularly at the sodium-potassium adenosinetriphosphatase (ATPase) pump because that is one of the regulatory devices for sodium and potassium in the brain. We found that stimulated sodium uptake in the brain cells is accelerated in females compared to males (Fig. 8) (18, 19). This leads to more brain edema. This is bad for survival because to compensate for hyponatremia the brain has to extrude sodium. So the males are more efficient at getting the sodium out, the females at getting it in. In potassium transport also, the males are better at getting potassium out of the brain. So the males are better at getting sodium and potassium out of the brain, which would lower brain osmolality and improve survival in hyponatremia.

In respect to the ATPase pump, the difference between males and females is entirely due to an ouabain-sensitive component that is much greater in the males (19). So males have much greater brain ATPase activity than do females, which enables them to pump out sodium and potassium, which are blocked by ouabain, and compensate for hyponatremia.

Hormonal differences can dramatically determine outcome (18). Using magnetic resonance spectroscopy, my colleagues and I studied changes in the three adenosinetriphosphate (ATP) peaks (alpha, beta, and gamma) and the phosphocreatine and inorganic phosphorus peaks (Fig. 9). In female rats at the height of their estrus cycle (when estrogen levels are highest) who are given an intraperitoneal dose of vasopressin, ATP is lowered by about 80%. The alpha, beta, and gamma peaks and the phosphocreatine peak are reduced to background levels. So there is no synthesis of ATP. Inorganic phosphorus is increased by about 500%. Measuring the intracellular pH by the ratio of inorganic phosphorus to phosphocreatine, the intracellular pH falls from 7.1 to 6.4. In a similar study with male rats from the same litter, and the same dose of vasopressin, nothing is changed.

So in rats given only a large dose of vasopressin without concurrent hyponatremia, the females, but not the males, undergo almost complete destruction of ATP synthesis, which is the fuel for the sodium-potassium adenosinetriphosphatase (ATPase) pump, and tremendous intracellular acidosis and brain edema, accompanied by 85% mortality in the female rats and no mortality in the males (18).

How to Treat Hyponatremia

Treat Fast? Treat Slow? Or about 1 Millimole per Liter per Hour? The raging controversy in the literature is on whether to treat hyponatremia fast, whatever that is, or slow, whatever that is, or somewhere in between. J. C. Ayus and I prospectively studied 45 patients divided into 2 groups, one that did not get demyelinating lesions and one that did (7). Both groups had similar serum sodium levels. The group without demyelinating lesions had a rate of correction about 1 mmol per liter per hour (Fig. 10). The group that did have demyelinating lesions had a similar rate of about 1 mmol per liter per hour. In the entire prior historical literature, the rate of correction is also about 1 mmol per liter per hour.

I think it's probably fair to say that the rate of correction simply isn't very important. I think that although there are so many arguments in the literature, the rate will probably turn out not to make any difference at all. An excellent paper by Worthley and Thomas (20) shows that correcting the sodium level at a rate of over 20 mmol per liter per hour, at least when the patient has a seizure, has no harmful effects. I do not recommend that rate, but point it out. I think that you can set a target of about 1 mmol per liter per hour, faster if the patient is more symptomatic.

Absolute Change in Serum Sodium. Although the rate of correction may not matter, some other things do. I think the most important thing we found—and a paper by J. C. Ayus shows it to be so in laboratory animals (21)—is that the actual delta, the absolute change, in serum sodium is indeed important (7). In the prospective study (7), the patients who had no lesions had an absolute change in serum sodium in the first day of less than 20 mmol/L (Fig. 11); those who got demyelinating lesions had a change more like 40 mmol/L per day; and patients recorded in the literature had a change of almost 30 mmol/L per day.

The absolute change in the serum sodium is important because a large change in serum sodium, whatever the rate, in the first couple of days is one thing that can lead to demyelinating lesions.

Some of the factors that we found lead to cerebral demyelinating lesions are, first and most important, an episode of anoxia or hypoxia, since cerebral blood flow is down when the patient actually stops breathing, and second (and also most important), a change in serum sodium of greater than 25 mmol in the first day of therapy. Overcorrection to hypernatremic levels can be quite dangerous in the initial couple of days of therapy. Patients who have blood-brain barrier defects, such as those with cirrhosis, even if they are not hyponatremic, are prone to hyponatremia when lactulose therapy is administered for hepatic encephalopathy. It could happen very easily because a huge amount of osmotic diarrhea is produced by using lactulose.

Rx. Putting the treatment prescription all together:

In patients without lesions, the rate of change in serum sodium in the first 12, 24, and 48 hours should be less than 25 mmol. Patients with demyelination usually have a much larger change, as shown historically and in our ongoing study. So I think that the most important cause of brain damage from hyponatremia is respiratory arrest.

Do not overcorrect the serum sodium level in a short period of time.

Perhaps more important: Prevent hyponatremia, particularly in young women.

Questions and Answers

Question: Given 100 women who are 34 plus or minus 6 years of age, what percentage of those women would suffer from postoperative hyponatremia, and are there any predictive clues or preventive mesures?

Saline, Not 5% Dextrose in Water, after Surgery

Arieff: An interesting question. Given 100 women who don't get hyponatremia, none of them will suffer any of these effects, and given 100 women who have a sodium level below 130 mmol/L, I cannot give you an exact figure, but many of them will suffer. So the best treatment is just to prevent it from happening.

I think that attention should be focused on the community standards that dictate the use of 5% dextrose in water after surgery. This is just a bad idea. The point is to use either Ringer's lactate, or normal saline, or something similar; then it will probably never happen. We're working on the use of vasopressin antagonists or estrogen antagonists to prevent this from happening. I can't provide the exact frequency of the syndrome, but if the patient doesn't get hyponatremic, it'll never happen. The best course is to prevent it from happening. Talk to your surgeons. Ask them to use saline.

Marvin Levitt: First I want to congratulate you on a stimulating and intriguing talk. What to me is so appealing is hidden in your last line. When a person presents a body of information in this perspective, in this fashion, there are as many questions as answers given. In this day of intensive medicine it's a pleasure for me to hear that every abnormality doesn't have to be immediately corrected.

I'm intrigued by certain questions your data presents. First, what would happen with postmenopausal women? Second, does the bladder in males absorb water? You implied that it might.

Finally, the ATPase story I find a little confusing because I think of ATPase as an enzyme that pumps potassium out and sodium in. You find that ATPase is responsible for pushing all cations in the cells, and as I recall ATPase pumps 3 potassiums in and 2 sodiums out. So I have a problem with that. But I think the data on the female is the first area in which I found that the male is more resistant than the female. I find it intriguing.

Postmenopausal Women

Arieff: I'll take your questions one by one. First, about postmenopausal women. That's an excellent question because we have been asked to consult on over a dozen postmenopausal women who get symptoms but don't as a rule suffer brain damage unless they are taking supplemental estrogens. I think this supports our findings in the isolated brain cell studies that one of the major culprits is in fact estrogen.

I'm sorry you misunderstood part of the data. That's probably my fault. The men weren't being cystoscoped, they were undergoing transurethral resection of the prostate, in which venous sinuses are actually opened and distilled water is poured into those open venous sinuses. This is why the men get hyponatremic. This is actually probably very common.

As for ATPase, it's a little bit different in the brain than elsewhere. In the brain it's largely an exchanger of sodium or potassium for hydrogen and amino acid. And the balance is toward the extrusion of sodium and potassium from the brain. The potassium can also exit by other channels. The sodium is largely a sodium-for-potassium and hydrogen exchange here. Your point is well taken for other tissues, but not so much for the brain.

Richard Gorlin: Where does the sodium go? Is it taken up by bone?

Arieff: No, it goes into the blood. Actually there's a misperception that the spinal fluid is the main brain extracellular space. The blood space is much larger. The sodium goes into the extracellular fluid and into the bloodstream. And the actual amount of brain sodium lost, in terms of total body economy, is very small.

Gorlin: How about the total body sodium?

Arieff: The cell is simply swollen with water; in other words, you have near-normal electrolyte content. We've actually worked this out in laboratory animals, and there is initially no loss of electrolyte at all. The brain's compensatory action begins probably in about 4 hours to actively extrude sodium, but initially it's just a gain of water, which is why it's so devastating in the first couple of hours when it occurs.

Richard Stein: Our experience here is much more with older patients developing hyponatremia. Of course there's the usual number of cardiacs and cirrhotics. However, the ones that we've seen who were symptomatic are often patients from nursing homes, elderly patients. I have a vague recollection that it is much more common in women than men. We haven't seen very many patients in this younger age group; I have seen one. In any event, the patients we encounter are primarily elderly women coming in from nursing homes with varying degrees of obtundation. We have just not seen this younger group, and I don't recall that we've had major morbidity and mortality in our patients. Perhaps our house staff use a variety of regimens you recommend to prevent or correct this.

I thought your last point about the magnitude of the correction in 12 to 24 hours was particularly interesting. You didn't actually give us an explanation for the mechanism of why that would produce so much difficulty. If it isn't the rate or the magnitude, could you elaborate?

Arieff: I think probably one of the reasons you are not getting as much mortality or morbidity is that these are older women who are postmenopausal and usually don't have as much estrogen.

The magnitude of correction is important. Stern (3) showed this in laboratory animals a long time ago, and it has been confirmed. When you have a hyponatremic brain, the electrolyte level is low and the brain may be swollen. If you abruptly increase the sodium level by a large magnitude, the brain is simply unable to compensate. It will shrink abruptly and violently and tear blood vessels, resulting in intracerebral hemorrhage. This in fact is what's been shown to happen—like Finberg's experiments (22) with cats. Intracerebral hemorrhage is what you get if you correct hyponatremia by too large a magnitude. The brain is able to compensate for almost anything within about 25 millimoles in either direction. This has been well shown in laboratory animals. So magnitude seems to be most important.

Stein: I'm conceptually having dificulty understanding why the rate of correction and magnitude aren't in some way related.

Arieff: They are not totally unrelated, but you can bring the sodium up by 25 millimoles at any rate, in other words, you can do 24 millimoles in the first hour—a huge rate—but nothing will happen. Whereas if the magnitude is 50 millimoles in the first two days, the patients will probably all die. So the distinction is not complete, but in general, magnitude is the more important area.

Question: (inaudible)

Arieff: I thought it was all inorganic phosphorus. In other words, because there was an impairment in phosphocreatine regeneration, and thus ATP synthesis, there is a huge accumulation of inorganic phosphorus. The phosphocreatine peak ran together with the inorganic phosphorus to make one peak.

Question: Is there a relationship between vomiting of pregnancy and brain edema?

Arieff: That would be an interesting thing to study now that we have CT and MRI readily available. I don't know of any data on that at all. An interesting question.

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The Puzzles of Unstable Angina Pectoris

Richard Gorlin

UNSTABLE angina is a clinical syndrome which poses intriguing questions, beginning with the problem of producing a correct definition of the condition. Nearly 20 years ago my group adopted the term "intermediate coronary syndrome" (1) because it stood for nothing in particular and thus indicated that the syndrome had diverse origins and presentations.

Three clinical entities must be distinguished:

- New-onset angina or ischemia.
- Intensification of preexisting angina or ischemia
- Protracted, often recurrent angina or ischemia at rest.

A newly proposed classification system (2) offers no less than nine subclasses of unstable angina. Yet the three subgroups listed above provide an easily remembered quick framework for categorizing the clinical pattern.

Historical Evolution of Etiologic Concepts. The causes of unstable angina have only recently been clarified and are still incompletely understood. Twenty years ago the ischemia was attributed to excess hemodynamic activity, impaired oxygen transport, or hypermetabolism (1, 3). Most patients, but not all, had elevated blood pressure or heart rate, or both. Angina without hemodynamic change or extracardiac factors remained unexplained until Moise (4) and Neill (5) described the progression of coronary stenosis in the period preceding an acute coronary syndrome. This reintroduced consideration of a vascular component, but it was the work of Davies (6) and Falk (7) that truly shifted the emphasis to the coronary artery itself. They described fissuring of atheromatous plaques, often with an overlying acute thrombus protruding into the lumen. This acute complex vascular lesion could obstruct, progress, or resorb. The lesion could also be a source of microemboli or could generate factors capable of inducing local vasoconstriction.

Relationship between Clinical Syndromes and Etiologic Factors

The possible contributions of myocardial and selected vascular factors to each of the clinical ischemic syndromes vary (Fig. 1).

New-onset angina is most likely related to progressive or stepwise arterial luminal narrowing, perhaps by progressive, cumulative, organized thrombus, but it can be provoked by any hemodynamic load. Small repeated intimal injuries with thrombotic repair and luminal narrowing may be the major precursor of new angina. This is even more the case when angina is intensified or "destabilized." This is clinically recognized by change in the tempo or severity of pain, intolerance to prior levels of medication or to a formerly acceptable physical load, or the appearance of a new precipitating factor.

Rest angina, whether protracted, or recurrent, or both, generally implies a major vascular component, especially plaque fissure and acute thrombus with or without obstruction. This is possibly accompanied, if not superseded, by microvascular embolism or constriction. Augmented cardiac activity as evidenced by hypertension, tachycardia, or evidence of increased contractile state is often observed, especially in comparison with the patient's own baseline (1, 3). Among the

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Adapted from the author's Grand Rounds in Medicine presentation November 7, 1989 at Mount Sinai Medical Center. From the Samuel Bronfman Department of Medicine, Mount Sinai Medical Center, New York. Address reprint requests to the author, who is Chairman of the Department and Murray M. Rosenberg Professor, at Box 1118, One Gustave L. Levy Place, New York, NY 10029.

most common metabolic factors, particularly in the elderly, is diminished oxygen transport secondary to the anemia of long-term blood loss. The anemia itself may not have been detected until a new or more severe anginal episode (triggered by defective oxygen transport) brings the patient to acute medical attention. Hyperthyroidism, with its hypermetabolic state, may be discovered in the same way.

The clinician's first obligation is to rule out such noncoronary causes of chest pain. Yet because of the rush to the catheterization laboratory in emergency admissions to hospital, it may be some hours before anemia or hyperthyroidism is discovered.

Acute Vascular Lesions. The majority of admissions to coronary care units are to rule out myocardial infarction. There is often an acute change (Fig. 2) in coronary pathology in patients with protracted rest angina. Ambrose (8) has identified new obstructed lesions in coronary arteries formerly shown to be patent although minimally diseased. Culprit vascular segments are usually long and irregularly scalloped, conditions which seem to be particularly thrombogenic. Yet the obstructing thrombus usually does not completely occlude the lumen.

The events that occur acutely are incompletely understood but can be inferred from various angiographic studies of the last decade. In a recent Canadian study (9), angiograms taken at the onset of unstable angina were compared with those performed about a week after the initial event. Relatively early after the clinical syndrome begins, many patients have either recognizable intraluminal thrombi or the complex vascular morphology of irregularly shaped, abruptly scalloped, intruding arterial segments. Those patients who came to emergency arteriography owing to clinical ischemia exhibited the highest frequency of thrombus. Remote from the event, the frequency of thrombi is much lower, but about the same number of vessels have the complex morphology.

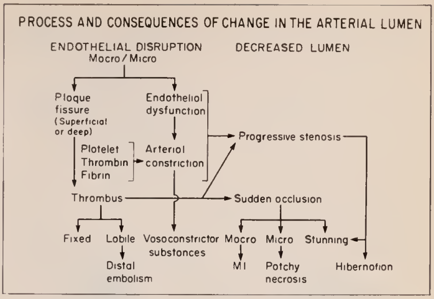
PROCESS AND CONSEQUENCES OF CHANGE IN THE ARTERIAL LUMEN
ENDOTHELIAL DISRUPTION
Mocro / Micro
DECREASED LUMEN
Ploque fissure (Superficiol or deep)
Endotheliol dysfunction
Plotelet
Thrombin
Fibrin
Arteriol constriction
Progressive stenosis
Thrombus
Sudden occlusion
Fixed
Lobile
Distal embolism
Vosoconstrictor substonces
Mocro
MI
Micro
Potchy necrosis
Stunning
Hibernotion

Fig. 1. The acute vascular lesions. Decrease in lumen size that reduces coronary flow may be sudden or progressive, total or partial. It begins with endothelial disruption, either macroscopic or microscopic. Although plaque fissure in this syndrome is usually superficial, platelets and fibrin accumulate over it, leading to thrombus formation. Thrombus is not always fixed but is often labile and, if nonocclusive, may shed emboli. The thrombus itself, or process of atherosclerosis, may lead to endothelial dysfunction. Blood vessel wall is remarkably sensitive to changes in endothelium, and constriction of artery can occur. In unstable angina, any of the underlying processes can extend beyond simple obstruction at site of plaque rupture or thrombus. Consequences for myocardium may be reversible contractile dysfunction.

Thus, thrombus (but not necessarily occlusion) is clearly responsible for much of what we

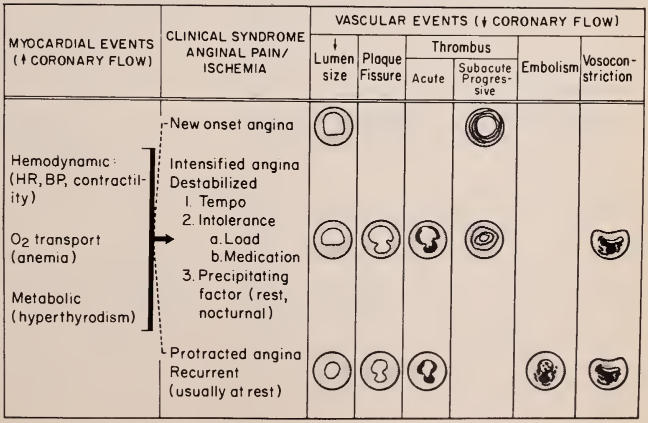
MYOCARDIAL EVENTS (↑ CORONARY FLOW)
CLINICAL SYNDROME ANGINAL PAIN/ ISCHEMIA
VASCULAR EVENTS (↓ CORONARY FLOW)
↓ Lumen size
Plaque Fissure
Thrombus
Acute
Subacute Progressive
Embolism
Vosoconstriction
Hemodynamic: (HR, BP, contractility)
O2 transport (anemia)
Metabolic (hyperthyrodism)
New onset angina
Intensified angina
Destabilized
1. Tempo
2. Intolerance
a. Load
b. Medication
3. Precipitating factor (rest, nocturnal)
Protracted angina
Recurrent (usually at rest)

Fig. 2. Possible contributions of myocardial and selected vascular factors to different clinical ischemic syndromes.

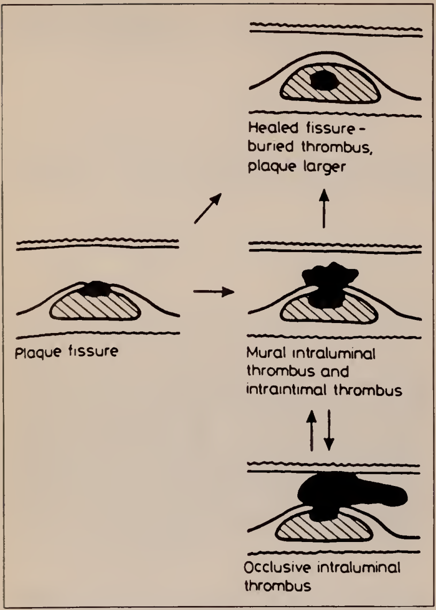

Fig. 3. Evolution of plaque fissure. Fissure may either reseal and stabilize or progress to thrombotic occlusion. Reprinted with permission from Davies et al (7).

identify as unstable angina. But the thrombus may have a role well beyond impedance to large artery flow.

Another puzzling observation seen in virtually every study since my own with Fischl and Herman (1) is that a small percentage of patients have apparently normal large coronary arteries. It is not known if these vessels are morphologically normal, if a complex lesion with thrombus had "remodelled" by the time of angiography, or if the ischemic syndrome related to constriction of the large (or even small) coronary arteries.

This leads us to consider the "reactivity" of coronary arteries. Normal coronary arteries exhibit smooth muscle relaxation and vasodilation in response to an endothelium-dependent agonist, such as acetylcholine (10, 11). Atherosclerotic arteries, on the other hand, paradoxically exhibit constriction (10, 11). Such constriction occurs not only at the site of stenosis but elsewhere in the diseased artery as well. This implies that atherosclerosis per se leads to endothelial dysfunction and perhaps to inappropriate smooth muscle constriction in response to those mediators which act through the endothelium. In the presence of plaque fissure and fresh thrombus, the propensity to vasoconstriction is even greater. Platelet-generated serotonin, thromboxane, and other byproducts of the thrombus all conspire to provoke local vasoconstriction (12). The endothelium itself may release endothelin (13), probably the most powerful vasoconstrictor known, along with other moieties.

Postmortem studies by Falk and co-workers (7) reported platelet adhesion and downstream embolization in the presence of atherosclerotic plaque. Something about the stenosis led to accumulation and intermittent occlusion by platelet masses (Fig. 3). Contrary to the situation in acute myocardial infarction, embolism will most likely occur when the coronary artery is only partially obstructed, allowing persistent, or at least intermittent, blood flow. This flow may "scour" platelet masses off the surface of the thrombus. Experimental work by Badimon et al. (14) documented that increased shear rate and blood flow over stenotic lesions in de-endothelialized vessel wall affect platelet behavior. Platelet adhesion to vessel surfaces increased, followed by time-related release of platelet mass, and thus downstream embolization. Flow patterns seem not only to affect the development of atherosclerotic plaque but also to cause changes in endothelium, augmented platelet deposition and adhesion, and finally, embolization.

Although the significance of such lesions is still unknown, they have been found downstream from the larger, incompletely obstructive culprit lesion in nearly all cases and present a picture quite different from that seen in myocardial infarction. Such intermittent fragmentation of platelet emboli may block blood flow in the small vessels distal to the thrombus or release vasoactive substances locally, producing small areas of patchy intramyocardial ischemia, necrosis, and ensuing clinical pain syndromes.

Overall Demand-Supply Concept. Physiologically, in the chronic stage of stable angina, whenever hemodynamic demand exceeds the coronary flow reserve, ischemia, and sometimes angina, results (Fig. 4). If lumen size progressively decreases, as in developing atherosclerosis, the flow reserve diminishes. Thus, a lesser hemodynamic burden produces ischemia. This can be controlled with therapy that attenuates the hemodynamic response. This is not the case when either constriction or thrombus virtually annihilates the coronary flow reserve.

So the acute, active phase of angina is different from chronic stable angina in that reduction in flow leads to reduced segmental perfusion, possible altered metabolism of the diseased segment, and finally, reduced contractile effort which, however, is generally reversible. Scintigraphic studies at 0–6 hours show poorer perfusion scans than at 12–18 hours (15), indicating that a deficient blood supply is restored relatively quickly. The condition is also associated with regional glucose metabolism, evidence of functional tissue, even in the presence of inadequate blood flow (16). This is clearly different from what is seen with chronic angina or in a normal heart.

Augmented sympathetic nervous system activity has been documented (17) in unstable angina in which the heart itself produced more norepinephrine than a normal heart, or even the heart of a patient with stable angina in whom pain was provoked by pacing tachycardia. The neurohormonal mechanisms are not fully understood.

Effects on Myocardium. The acuity and severity of the vascular insult determines whether the myocardium shows evidence of damage or not. Katus et al. (18) have shown release of myosin light chains in patients who also exhibit ST-T or T wave changes. This may be a subtle marker of a necrotic stage and corresponds with the well-known poorer prognosis of patients with ST-T changes. Such patients have a 55% greater likelihood of undergoing bypass and angioplasty and of death than patients who have no ST-T changes (19).

Experimental studies show that myocardial contractility falls progressively with repeated brief coronary occlusion, even when followed by a period of reflow (20). By the sixteenth consecutive occlusion-reperfusion cycle the myocardium fails to contract at all. This has been called “myocardial stunning” because the short periods without flow have caused contractile function to cease, yet with time the contractility is recoverable.

Similarly, Matsuzaki et al. (21) produced partial coronary stenosis which caused a 50% reduction in regional systolic wall thickening or shortening. For over five hours the myocardium remained alive and functional although contracting at half of its former capacity (Fig. 5). This is analogous to what has been termed “hibernation” or down-regulation of contractility compatible with available flow and oxygen transport. After release of the partial stenosis, gradual recovery of segmental contraction occurred at between three and seven days. Such reversible ischemia seems to occur in unstable angina (Fig. 6). Coronary angioplasty has also effected segmental recovery of function on relief of stenosis in unstable angina (22). The capacity for recovery is much greater than in patients with either myocardial infarction or stable angina.

Unstable angina most likely is associated with reduced perfusion, altered metabolism, and diminished contractile effort. Is this due to myocardial stunning caused by intermittent closure and reperfusion, or is it hibernation due to down-regulation of contractility and contraction resulting from progressive, sustained reduction in blood flow? Whatever the case, the important point is that the effects on the myocardium are often reversible, and therapy should be so directed. In 1986 we (Gorlin, Fuster, and Ambrose)

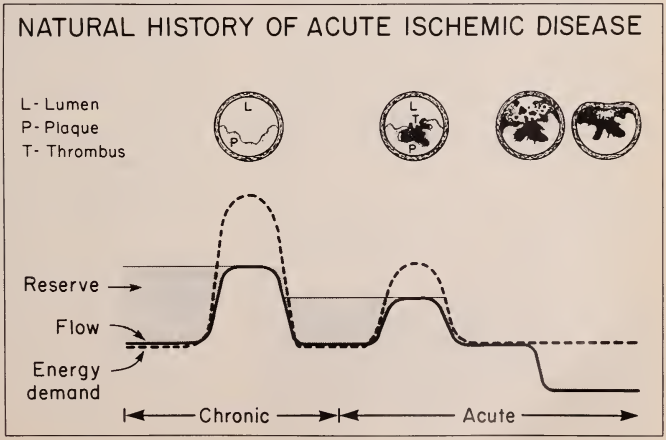

Fig. 4. Overall demand-supply concept.

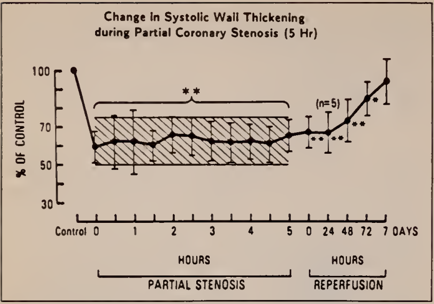

Fig. 5. Steady state of reduced wall thickening was maintained for five hours during partial coronary stenosis. Full recovery took 7 days. Reprinted with permission from Matsuzaki et al (21).

suggested that "time to reperfusion" following a short period of total occlusion may lead to the syndrome of unstable angina (23). This may not always be so. Blood flow may be "chronically" depressed, especially at a microvascular level, in some patients without an intermittent no-flow, reflow pattern.

Therapy

Patients with first-onset unstable angina or active, intensified angina are often a major diagnostic puzzle. There may be only a pain syndrome, with normal physical examination, ECG, and enzyme levels. Is the pain cardiac in origin (especially if symptoms are of new onset)? If the discomfort is not new but is intensified (Fig. 2), the clinician must search for factors that precipitated the change. The commonest is an extracoronary factor, such as anemia or hypermetabolic state or, for reasons not understood, augmented sympathetic activity with hypertension or tachycardia. Any or all may potentiate ischemia in the face of a previously clinically silent, progressive coronary stenosis.

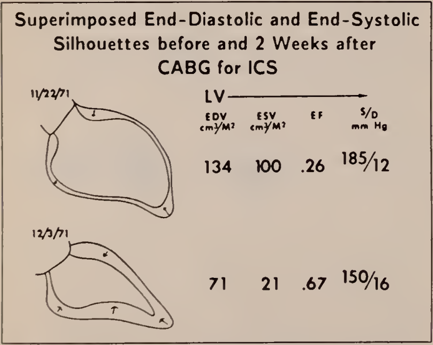

Fig. 6. Sequential ventriculograms (left ventricle, LV) made during and after acute coronary ischemic event. Poor ejection fraction (EF) and enlarged heart (upper panel) resolved two weeks after coronary bypass surgery (CABG), and contractile pattern and ejection fraction are normal (lower panel). ICS, intermediate coronary syndrome; EDV, end-diastolic volume; ESV, end-systolic volume; S/D, systolic/diastolic. Reprinted with permission from Fischl et al (1).

If the onset has been heralded by rest pain, whether protracted or recurring or both, what is suggested is epicardial coronary artery occlusion by a variety of mechanisms (detailed above), or downstream small-vessel ischemia through either emboli or vasoactive substances washed off the acute coronary lesion complex.

Because the etiology of the syndrome is so complex, therapy must be directed at each component, emphasizing the element that seems dominant (anemia, versus large-artery recurring thrombosis, versus vasoconstriction). One must recognize that ischemia may persist, even with an open coronary artery, and that thrombus and fissured plaque may generate emboli and vasoactive factors as well as impede blood flow.

Therapy has three aims: first, reducing hemodynamic activity; second, enlarging coronary artery caliber and inhibiting constriction; and third, attenuating active thrombus formation.

Aim 1: Reducing Hemodynamic Activity. Reduction of hemodynamic activity to normal or less than normal levels has been accomplished effectively with beta adrenergic blockade (1, 24), especially when heart rate and blood pressure are elevated. Contractility may also be augmented in some patients, as evidenced via ventricular imaging, and may relate to the hypercatecholaminic state (17). Although many patients will respond to beta-blockers, nitrites and calcium channel blockers are also effective. They may act partly through reduction in ventricular loading conditions.

Aim 2: Enlarging Coronary Artery Caliber and Inhibiting Constriction. Both nitrites and calcium blockers can enlarge coronary artery caliber and inhibit locally induced large (and small?) vessel constriction (25, 26). Distante et al. (25) found intravenous isosorbide dinitrite to be especially useful in patients refractory to other measures. There is great uncertainty as to the role of macro- or micro-vascular constriction in this disorder, but an advantage of the use of nitrites lies in the fact that they induce dilation independently of the endothelium. The latter is obviously damaged, at least locally, and may actively contribute vasoconstrictor substances, effecting local as well as downstream vascular smooth muscle constriction.

Aim 3: Attenuating Active Thrombus Formation. Nearly 30 years ago Wood (27) recommended heparin for unstable angina, and Telford (28), in a small series of patients, found heparin superior to beta blockers. Recently, Théroux et al. (29) studied the effects of heparin and aspirin (administered both separately and together) in unstable angina. Heparin alone was correlated most highly with a lower incidence of future myocardial infarction and with reduction in refractory angina compared with aspirin, although not all investigators agree on its symptomatic efficacy. Nonetheless, aspirin has a major role in the late follow-up period after an episode of unstable angina (30).

Thus, there appears to be a clearcut role for both anticoagulant therapy and aspirin in early unstable angina, aspirin being useful for its posthospitalization effects on death and reinfarction.

Thrombolysis would seem to be a logical avenue of therapy in this syndrome, owing to the frequent presence of thrombus demonstrated angiographically and angioscopically, but results are inconclusive to date. Angiographic regression occurs in some patients but not in others, whereas clinical remission occurs in only a few. Whether this is due to timing, to age of thrombus, or to a different role for thrombus in the syndrome is unknown (see below). So at this point thrombolysis appears to have limited value in the treatment of unstable angina (31).

The role of microvascular platelet-fibrin embolism remains unknown but could account for evidence of ischemia when the larger coronary artery is open and blood is flowing, even in the presence of a clot. The effects of antithrombotic, antiplatelet, and anticoagulant therapy on the microvascular component of ischemia are undefined.

Interventions in the Acute Phase. Since this syndrome is not associated with high mortality, should we intervene in the acute phase? Indeed, when ischemic symptoms are refractory, they should be treated pharmacologically according to the principles outlined above.

The intra-aortic balloon pump has been effective in refractory cases of angina but always leads to the question of what comes next, because the patient usually becomes pump-dependent.

Revascularization should be delayed when clinically feasible.

Angioplasty is effective, but the incidence of abrupt closure is high when the procedure is done in the midst of an acute coronary syndrome. It also carries the significant risk of causing distal coronary emboli, and the three-to-six-month restenosis rate of 24%–40% must always be factored into any decision. Morbidity from the procedure is much less if it can be delayed until after the first 7–10 days.

The same is true for coronary bypass surgery. Kaiser et al. (32) have proposed a set of criteria by which to judge whether bypass will achieve the best possible result in unstable angina:

- admission to coronary care unit to rule out myocardial infarction.
- prolonged or rest angina
- ST-T changes
- intravenous nitroglycerine or heparin
- new or changing anginal pattern
- pain after myocardial infarction
- intraaortic balloon counterpulsation

Generally, only patients whose pain is refractory to the standard forms of treatment should be considered for early surgery or angioplasty.

The Puzzle of Nonocclusive Thrombosis and Endothelial Injury and Dysfunction

The most puzzling aspect of unstable angina is thrombosis. Why is it not seen in every patient —simply because thrombus is not detected by current angiographic techniques, or has the thrombus lysed spontaneously by the time angiography is performed?

Alternatively, was thrombus never there at all, and has the syndrome arisen from some other cause in some patients? In fact, about 10%–20% of patients with unstable angina have ostensibly normal epicardial coronary arteries at angiography. Although the last is infrequent, if there is no clear relationship between clot dissolution and the clinical picture, does that mean that the thrombus is not causing the syndrome by obstructing a large coronary artery? Is the syndrome related in some instances to repetitive embolization of thrombus or to induced local or downstream microvascular vasoconstriction provoked by an unstable arterial wall lesion, endothelium, thrombus, or both? Is the hemodynamic or local cardiac sympathetic element more prominent than formerly estimated? Since all patients do not have even partial intracoronary thrombus, and since thrombolytic therapy fails to relieve the majority of clinical events, obstructing thrombosis may not be the sole factor in the production of myocardial ischemia. The lesion itself may be an embolism generator as well as a stimulus to vasoconstriction of an already damaged arterial wall.

The unstable ischemic syndrome, then, must be viewed as the product of a complex lesion acting in a dynamic pathophysiologic domain rather than merely as the result of an occluded blood vessel.

Does this imply that there has been a preceding event, an activation or destabilization of the arterial endothelium? In studies of silent ischemia and its progression to acute ischemic syndromes, questions arise about whether an ongoing endothelial process may antedate the clinical event (33). The endothelium may be damaged in some fashion by atherosclerosis, by oxidation products of lipoproteins, or by byproducts of locally induced inflammation, as during intercurrent infection. These pathological events may "activate" a vulnerable endothelium.

Unstable angina may be the clinical end point of recurring bouts of clinically silent ischemia precipitated by endothelium-generated intermittent arterial contraction, or intermittent production of platelet thrombi, or both. Products of platelet or thrombin activation have been reported in unstable angina (12, 34). Moreover, active vasoconstriction itself, or frequent bending of an active cardiac artery, can lead to endothelial damage and secondary platelet attachment to endothelium, and thus, by a reverse sequence of events, lead to endothelial damage (35). Focusing on these aspects of the problem will probably produce the most valuable insights into this intriguing condition.

Conclusion

Unstable angina still remains an enigma. Even the definition is ambiguous. The syndrome has at least two recognized major causes: a sudden or progressive increase in cardiac metabolic activity, and reduced myocardial blood flow. Both may be present. There is now identified an acute change in the endothelium with fissuring of atherosclerotic plaque, with superimposed, often nonocclusive thrombus, and finally, local coronary vasoconstriction and downstream microvascular embolism. The myocardium rendered ischemic by these processes may resemble stunned or hibernating myocardium; therefore, recovery of function is often possible if perfusion can be reestablished in time.

The issue of whether primary endothelial disease or dysfunction initiates the process should be the subject of further investigation.

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A Clinical Approach to Lyme Disease

Robert B. Nadelman, M.D., and Gary P. Wormser, M.D.

Abstract

Lyme disease (also known as Lyme borreliosis) is an emerging, newly described infectious disease with diverse clinical manifestations. The disease is caused by the spirochetal agent *Borrelia burgdorferi,* which is transmitted to humans by the bite of certain species of *Ixodes* ticks harboring the organism. The most readily identifiable clinical feature is the distinctive skin lesion, erythema migrans. If recently infected patients go untreated, approximately 15% will develop neurologic conditions (most commonly facial nerve palsy), 8% will develop myocarditis (typically with heart block), and 60% will develop migratory mono- or pauci-articular arthritis. Diagnosis depends on clinical suspicion, recognition of the characteristic signs and symptoms, and appropriate testing for antibody to *B. burgdorferi.* Serology for Lyme disease, although in need of better standardization, is most useful in diagnosing patients with manifestations of Lyme disease other than erythema migrans. All manifestations of Lyme disease are potentially treatable with either a beta-lactam antibiotic (for instance penicillin, amoxicillin, or ceftriaxone) or a tetracycline preparation. However, the optimal antimicrobial regimen, including choice of drug, drug dose, route of administration, and length of therapy, is unknown. Other important areas for future research include *Ixodes* biology and control, improved laboratory tests for diagnosis and for assessing response to therapy, and vaccine development.

CERTAIN species of *Ixodes* ticks that carry the newly recognized spirochete, *Borrelia burgdorferi,* pose an increasing and potentially serious environmental threat for millions of people whose activities of daily living place them at risk for tick bites. Lyme disease, or Lyme borreliosis as it is known in Europe, the consequence of *B. burgdorferi* infection, is now the most common tick-borne illness in the United States and the most common borrelial infection in North America (1).

Lyme disease is a systemic illness with a multiplicity of clinical manifestations. Although certain aspects of the illness were recognized as early as 1909 in Sweden (2), it was only recently discovered that what appeared to be several distinct clinical entities were really part of the clinical spectrum of a single infectious disease. This can be attributed in part to the insight of two Connecticut mothers who in 1975 alerted the local health department about an "epidemic" of "juvenile rheumatoid arthritis" in the vicinity of Lyme, CT (3). Since that time our understanding of the tick vectors, the etiologic bacterium (*B. burgdorferi*), the diverse clinical features, and the treatment of Lyme disease has grown considerably.

In this review we outline our approach to diagnosis and treatment. Limitations in present knowledge are discussed and priorities for future research indicated.

Transmission

Three species of *Ixodes* ticks in the United States are known to transmit *B. burgdorferi* to humans: *I. dammini* in the Upper Midwest and Northeast, *I. scapularis* in the South, and *I. pacificus* on the West Coast (4). Over the past decade, populations of *I. dammini* have increased dramatically, particularly in the northeastern coastal United States from Massachusetts to Mary-

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land and along the Wisconsin-Minnesota border (1). Reforestation of old farms, and the resurgence of the deer population, which thrives in these wooded areas in the absence of predators, have likely contributed to the rapid growth of the *I. dammini* population (5) (see below). Populations of *I. scapularis* and *I. pacificus* appear to have remained more stable (6). It is fair to say that Lyme disease is epidemic throughout much of the range of *I. dammini*, endemic on the West Coast, and sporadic throughout the South. At least 43 states have reported indigenous cases of Lyme disease (1), as have Canada (7), most European countries (8), China (9) and Japan (10), and Australia (11).

TABLE 1

Prevalence of Spirochete Infection in Ixodes dammini *by Stage in Westchester County, N.Y., 1987–1989**

Tick Stage	No. infected/ no. examined	Prevalence of infection
larva	3/325	0.9%
nymph	84/365	23.3%
adult	81/159	50.9%

* Durland Fish, unpublished data.

The life cycle of the tick consists of three feeding stages (Fig. 1), but the second or nymphal stage of the tick is the principal vector for transmission of *B. burgdorferi* (12). This may appear surprising since the adult (third) stage is more likely to be infected with *B. burgdorferi* than the nymphal stage (Table 1). A major reason for this unexpected finding is that the much smaller size of the nymphal tick (about that of a poppy seed) enables it to bite a person and feed on human blood for several days without detection (Fig. 2); less than one in three patients with early Lyme disease even recall a tick bite (13, 14). The adult female tick (Fig. 1) is about the size of an apple seed, and although it also may cause Lyme disease, it is more likely to be noticed and removed before transmission of *B. burgdorferi* can occur (usually ticks must feed for at least 24 hours to transmit *B. burgdorferi* in an animal model [15]). Yet to be defined factors other than duration of feeding may also play a role in facilitating transmission, since less than 5% of nymphal *Ixodes* bites in humans transmit sufficient *B. burgdorferi* to result in clinical infection (16–18).

Although the white-tailed deer (*Odocoileus virginianus*) is intimately involved in maintaining the life cycle of *I. dammini* ticks, the reservoir of *B. burgdorferi* in nature is not deer but other woodland mammals, such as the white-footed mouse (*Peromyscus leucopus*) (19) (Fig. 3).

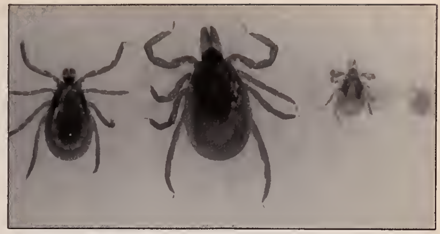

Fig. 1. The stages of *Ixodes dammini:* (from left to right) male and female adults, nymph, and larval forms. Female and nymph are involved in transmission to humans of Lyme disease. Reprinted with permission of Pfizer Central Research.

Newly hatched *Ixodes* larvae are usually spirochete free, because *B. burgdorferi* is infrequently transmitted transovarially (20, 21) (Table 1). Larvae may become infected if their first blood meal is taken from a host spirochetemic with *B. burgdorferi* at the time of the bite. The tick then molts, overwinters, and emerges in June or July as a potentially infectious nymph. After a second blood meal, the nymph develops into an adult that typically feeds on deer (resulting in the common name for this tick species in the Northeast, the "deer tick"), but may also bite and infect humans or other mammals. The engorged female mates with the male while feeding, and on engorgement drops to the ground, where she deposits eggs in the spring to complete the two-year life cycle.

Clinical Manifestations

Symptoms typically begin from three days to a month after a tick bite, the average incubation period being about one week (13, 14).

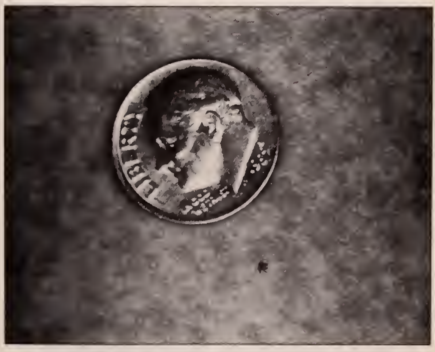

Fig. 2. Engorged nymphal *I. dammini* feeding on a human arm. Note relative size of nymph in comparison to dime and to patient's freckles.

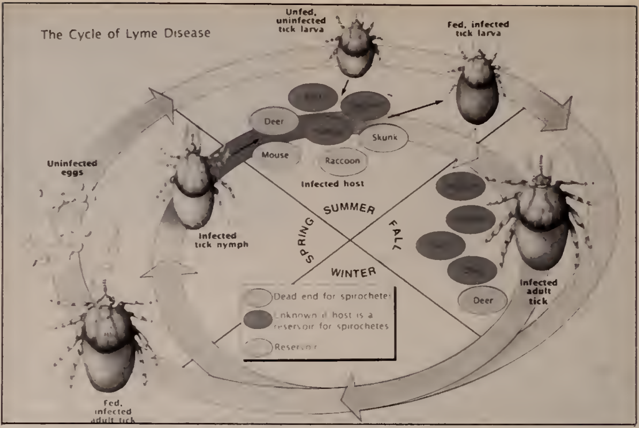
The Cycle of Lyme Disease
Unfed, uninfected tick larva
Fed, infected tick larva
Deer
Mouse
Skunk
Raccoon
Infected host
Uninfected eggs
Infected tick nymph
SUMMER
SPRING
FALL
WINTER
Dead end for spirochetes
Unknown if host is a reservoir for spirochetes
Reservoir
Deer
Infected adult tick
Fed, infected adult tick

Fig. 3. Life cycle of *Ixodes dammini*. Reprinted with permission from Daniels TJ, Falco RC, The Lyme disease invasion, *Natural History* 1989; 99:8.

Lyme disease has been described as occurring in three clinical stages. However, this classification (Table 2) may be problematic for a number of reasons. Symptoms in each stage may overlap, and all three stages need not occur in any one individual. For example, arthritis, usually a late manifestation of Lyme disease, may occur in the absence of prior clinical illness (without prior erythema migrans or recognized flulike illness). Many patients who are seropositive for *B. burgdorferi* are completely asymptomatic and do not clearly fit into any stage. Furthermore, there is insufficient evidence to base treatment modality on stage alone.

An alternative classification scheme (22, 23) divides manifestations of Lyme disease into early and late, "late" defined as occurring more than one year after infection. Using this classification, most cases of Lyme arthritis would be considered "early Lyme disease," although in common parlance this manifestation is usually considered "late Lyme." However, it is often impossible to date the time of onset of infection, making the use of this classification scheme difficult. We do not feel that there presently exists an adequate classification system, and therefore base our classification of patients on their specific clinical manifestations.

Erythema Migrans and Early Disease. The rash considered pathognomonic for Lyme disease is known as erythema migrans (Figs. 4, 5). Starting at the bite site, a reddish papule develops;

TABLE 2

Classification Schemes for Lyme Disease

Systems	Categories	Clinical Manifestations
Staging	Stage 1	Erythema migrans
	Stage 2	Multiple erythema migrans lesions Meningitis Cranial neuritis Radiculoneuritis Myocarditis Brief arthritis attacks
	Stage 3	Prolonged arthritis attacks Chronic encephalomyelitis Chronic axonal polyradiculopathy Acrodermatitis chronica atrophicans Debilitating fatigue
Early vs. Late	Early	Stages 1 and 2 above
	Late	Acrodermatitis chronica atrophicans Chronic joint/bone manifestations Chronic neurologic manifestations

over a period of days it rapidly enlarges, often with central clearing or peripheral darkening, until it becomes an oval or circular macular lesion (often with a tiny central eschar at the bite site). Lesions may range in size from that of a quarter to more than 20 cm in diameter. Local pain and pruritis may occur but usually are not prominent.

It is important to recognize the various possible configurations of the rash, ranging from homogeneous erythema to targetlike lesions, with or without irregular shapes, bluish discoloration, or vesiculate centers (13, 14, 22).

In the United States, approximately 15% of patients will have additional smaller lesions at other cutaneous sites (Fig. 5), presumably secondary to seeding of the skin during spirochetemia. An individual lesion is often present for days to weeks (13, 14), sometimes even longer (22). If untreated it will spontaneously disappear within several weeks but may recur (13, 22).

The rash must be distinguished from poison ivy, tinea infection (ringworm), streptococcal or staphylococcal cellulitis, contact dermatitis, and even herpetic infection. Most importantly, the rash should be differentiated from an intense local reaction to the tick bite, which tends to occur within a day of the bite, is usually smaller than the size of a quarter, regresses within a day or two rather than expands, and is associated with an uncomplicated course. The propensity for the rash to occur at sites uncommon for routine bacterial cellulitis such as the axilla, groin, or popliteal space is a helpful feature in differential diagnosis (Figs. 4, 5).

The rash may be unaccompanied by other symptoms, or more commonly, as in 60%–80% of cases (13), may be associated with a flulike illness—fatigue, myalgias, arthralgias, headache, nausea, fever, and chills—that may recur intermittently. Diarrhea and nasal and respiratory complaints are reported infrequently. The rash may be absent, or it may be overlooked if it occurs on a part of the body where it is difficult to see, such as the buttocks, back, or popliteal fossa (Fig. 4). In such cases, Lyme disease may easily be confused with nonspecific viral syndromes.

Cardiac Disease. From weeks to months after the tick bite, approximately 8% of untreated patients may develop cardiac disease (24, 25). In our experience, cardiac involvement, as characterized by an electrocardiogram demonstrating heart block, is already present in 2%–3% of patients referred just for erythema migrans (26). In the few instances in which pathologic material has been available, myocarditis, sometimes in association with spirochetes morphologically typical of *B. burgdorferi,* was present (27–29). Pericarditis may also be found (24), but valvular disease and endocarditis are extremely rare or nonexistent. Their absence may help to distinguish Lyme disease from rheumatic fever. Clinical manifestations when present include dizziness, syncope, palpitations, chest pain, or dyspnea.

Varying degrees of heart block are characteristic, including life-threatening complete heart block (23, 28). Block is typically at or above the atrioventricular node but rarely may occur more distally (25, 30, 31). Isolated instances of cardiomegaly and myocardial uptake on gallium scan (24, 28, 30) have been observed. Although cardiac complaints are generally present in early illness and are self limited, one recent report described a patient with cardiomyopathy of several years' duration associated with histologic, serologic, and microbiologic evidence of *B. burgdorferi* infection (29).

Neurologic Disease. Neurologic involvement occurs in 15% of patients with untreated early Lyme disease, usually weeks to a few months after tick bite (32–34). But it has been recently recognized that certain neurologic manifestations may only first appear several years after infection (23, 32, 35).

Neurologic examination most often will reveal cranial nerve palsies or signs of radiculopathy, but a wide variety of other neurologic findings (Table 3) have been reported (23, 35–47). In 1941 Bannwarth described patients with the triad of meningitis, radiculitis, and cranial nerve palsy (48). We now know that these patients had Lyme borreliosis. Seventh nerve palsy, particularly if bilateral, is a hallmark of neurologic Lyme disease (23, 34, 36, 38, 39, 42, 49). At least some of these patients are spirochetemic at time of presentation (50). Patients with meningitis tend to have negative Kernig and Brudzinski signs (36). A Guillain-Barré-like syndrome (47) has been described associated with meningitis.

Depending on the specific neurologic manifestations of Lyme disease, cerebrospinal fluid may be normal, or may have a modestly elevated level of protein, mononuclear pleocytosis, and a glucose level that is normal to mildly depressed (33–36, 39, 42). *B. burgdorferi* has been grown from cerebrospinal fluid (51–54), which may also contain mononuclear cells specifically responsive to *B. burgdorferi* antigen (53, 55).

Some patients with Lyme disease develop encephalopathy characterized by impaired concentration, depression, intellectual deterioration,

and personality change (23, 34–42, 44, 46). Cognitive dysfunction as measured by neuropsychiatric testing may be present, and may be reversible with treatment (40, 44). Onset of this manifestation of Lyme disease may occur many years after initial infection. A multiple-sclerosis-like illness (32, 34, 35) has also been described.

Peripheral neuropathy is an increasingly recognized "late" neurologic manifestation of Lyme disease. Abnormalities in peripheral nerve conduction associated with axonal damage (43, 56), and with infiltration of lymphocytes and plasma cells in perineural perivascular locations and in the nerve (56), have been noted. Nerve conduction abnormalities may improve with antibiotic treatment (43).

Spirochetes have not been recovered from neuronal lesions (43, 56). However, some patients with Lyme neuroborreliosis have been found to have an IgM antibody to *B. burgdorferi* that binds to human axons (57), raising the possibility of autoimmune-induced neurologic damage. Cerebrospinal fluid analysis in "late" neuroborreliosis may be normal or may resemble that in aseptic meningitis (23, 39, 40). Intrathecal production of antibodies to *B. burgdorferi* (44, 45, 58, 59) is inconsistently present. Although magnetic resonance imaging may show areas of demyelination or nonspecific bright patches (39, 40, 44), computed-tomography scan is less likely to be abnormal (46). Rarely, spirochetes have been visualized in brain tissue (56).

TABLE 3
Neurologic Manifestations of Lyme Disease

Cranial nerve palsy (esp facial nerve)
Radiculopathy
Meningitis
Encephalitis
Peripheral neuropathy
Plexopathy
Chorea
Mononeuritis multiplex
Transverse myelitis
Cerebellar ataxia
Pseudotumor cerebri
Guillain-Barré-like syndrome
Optic neuritis
Multiple-sclerosis-like illness
Seizures
Dementia
Cranial arteritis
Argyll Robertson pupil
Psychosis
Anorexia-nervosa-like illness
Headaches
Photophobia
Stiff neck
Dysesthesias
Paresthesias
Diplopia
Irritability
Poor concentration
Hearing loss
Sleep disturbances
Hemiparesis
Paraparesis
Emotional lability

Rheumatologic Disease. Months after initial infection (6 months on average), approximately 60% of untreated patients will develop migratory mono- or pauci-articular arthritis predominantly in the large joints, especially the knees (60), but smaller joints, including the temperomandibular, may also be affected. Although most such patients have a benign course, 5%–10% develop chronic destructive arthritis. These patients are more likely to have HLA type DR4, often combined with HLA DR3 or DR2 alleles (61, 62).

Joints are typically swollen, but neither very painful nor red. Baker's cysts may be seen occasionally; rheumatoid-like nodules are rare (22, 56, 63). One case of myositis has been described associated with severe myalgia, abnormal gallium uptake, electromyogram showing focal muscle denervation, and biopsy demonstrative of spirochetes in muscle despite normal creatinine phosphokinase levels (64).

Ophthalmologic Disease. Lyme disease may be associated with eye involvement (65–70); unilateral blindness has been described in one patient who developed panophthalmitis (65). Conjunctivitis is the most common form of ophthalmologic disease (66), but choroiditis with exudative retinal detachment (67), papilledema (68), pseudotumor cerebri (69), optic neuritis (66), and keratitis (70) have also been reported.

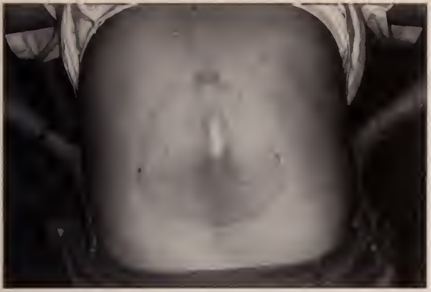

Fig. 4. Erythema migrans may go unnoticed by a patient when it occurs in certain body sites: **Left** In left axilla of a woman. Periphery of rash is lighter in intensity than center. **Middle** In left popliteal fossa. Intensely red center reminiscent of cellulitis. **Right** On lower back. Target-like erythema migrans.

Cutaneous Disease other than Erythema Migrans. In Europe, but not commonly in the United States, some patients with inadequately treated Lyme disease have developed a specific cutaneous process associated with thinning of the skin, usually of the extremities, known as acrodermatitis chronica atrophicans. *B. burgdorferi* has been recovered from such lesions (56, 71, 72). A plasmacytoid skin reaction due to *B. burgdorferi* infection known as lymphocytoma (22) is also more common in Europe than in the United States. Why these lesions occur more frequently outside the United States is unclear, although the observation does suggest pathogenic differences among strains of *B. burgdorferi*.

Lyme Disease during Pregnancy. Like syphilis, Lyme disease during pregnancy may be associated with congenital infection of the infant and resulting clinical illness. Several reports describe infants who died shortly after delivery, or were stillborn, to mothers who had Lyme disease during pregnancy (73–76). Spirochetes were found in autopsy specimens from some of these babies. Congenital heart defects and syndactyly have occurred in babies of mothers who had Lyme disease during pregnancy, but these associations are anecdotal (76). A small prospective study was unable to demonstrate a greater number of birth defects in babies born in a Lyme-endemic area than in babies born in a nonendemic area (77).

Diagnosis

Although the diagnosis of Lyme disease may be clinically apparent in a patient with erythema migrans or with the triad of aseptic meningitis, radiculitis, and facial nerve palsy, the diagnosis is frequently elusive and depends on a careful history, physical examination, and appropriate laboratory tests. Consider Lyme disease if there is abrupt onset of illness during late spring or summer in a previously healthy active person who either lives in or has visited an endemic area. Many patients have neither a history of a prior tick bite nor of travel specifically to a wooded area. In an endemic area the most likely source of exposure is often the patient's own back yard (78).

To distinguish Lyme disease from connective tissue illnesses, viral syndromes, multiple sclerosis, and other illnesses may require laboratory testing. Enzyme-linked immunosorbent assay (ELISA) and immunofluorescent assay (IFA) are the present standards (79). The ELISA has the advantage of being easier to standardize and to run on large numbers of serum specimens, and is less expensive. The IFA has the advantage of being titerable, which enables the physician to diagnose recent illness based on fourfold changes in antibody titer. Either test may be modified to specifically detect IgM or IgG antibodies. Other

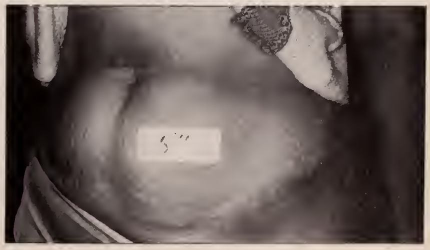

Fig. 5. Two target-like erythema migrans lesions on a patient's abdomen. Lesions had bluish centers. Secondary lesions are usually a result of hematogenous spread of *Borrelia burgdorferi* to skin.

tests, such as Western blot (80), hemagglutination (81), and ELISA capture assay (82), are not generally available at present.

False Negative Antibody Tests. Unfortunately, most patients are not able to mount an antibody response early in the disease; half or more of patients with EM have negative antibody tests (83–85). Antibiotic therapy may suppress an antibody response. In addition, for unknown reasons some patients are unable to produce detectable antibodies to the Lyme spirochete. In some of these patients, a specific T-lymphocyte proliferative response to *B. burgdorferi* antigen has been demonstrated (86). In some, cerebrospinal fluid antibody to *B. burgdorferi* has been detected in the absence of serum antibody (87).

A negative serologic or lymphocyte-stimulation assay should not necessarily preclude empiric treatment of Lyme disease for selected patients with highly suggestive signs or symptoms, such as the presence of erythema migrans or a facial nerve palsy of unclear cause in a person who lives in or has visited an endemic area.

Because of the problems with false negative antibody tests, alternative assays are under investigation. Although serum and urine antigen tests have not been successfully adapted for human specimens to date, and the polymerase chain reaction (88) remains investigational, some cases of Lyme disease have been detected by culture of blood (50, 51, 54, 89, 90), cerebrospinal fluid (51–54), synovial fluid (56, 91), or biopsied skin (51, 54, 90, 92) after incubation in BSK II, an enriched media (93). Cultures, however, are low-yield assays restricted to specialized laboratories (50).

False Positive Antibody Tests and Asymptomatic Seropositives. False positive antibody tests may also occur, particularly in patients who have other spirochetal disease, including syphilis, relapsing fever, and leptospirosis (94), but also in patients with mononucleosis (51, 95). A positive VDRL (or other test for cardiolipin antibody) is helpful in confirming the serologic diagnosis of syphilis and in excluding Lyme disease.

Patients with antibodies to *B. burgdorferi* without a history of Lyme disease may have false positive tests, but some apparently have asymptomatic infection. In fact, the ratio is believed to be one asymptomatic seroconverter for every patient with symptoms of early Lyme disease (96, 97). In some highly endemic areas, as in parts of Westchester County, NY, the prevalence of persons who are seropositive may exceed 5% of the total population (98). In such areas, positive Lyme serologic assay may be coincident with, rather than related to, a particular patient's symptoms.

In nonendemic areas, asymptomatic seropositives are likely to be false positives. Technical factors, inadequate quality control, and lack of standardization may be responsible for a significant fraction of false positive (99, 100) and false negative (101, 102) tests, a situation which can often be clarified by repeating the test or using a different assay method.

Treatment

Few well-controlled studies are available on which to base recommendations for treatment. Antibiotic testing has not been standardized for slow-growing organisms such as *B. burgdorferi* (101). Results of in vitro antibiotic testing may not be indicative of efficacy in humans; erythromycin, for example, is an antibiotic with excellent in vitro but less than optimal in vivo activity (103–105). Animal models of infection are imperfect substitutes for human disease, and antibiotic dosing in animals does not necessarily correlate with pharmacologically achievable levels in humans.

Penicillin and tetracycline preparations have been the mainstays of therapy (Table 4) and are the only antibiotics shown to be better than no therapy (106, 108). However, some patients' less than optimal response to these drugs (104, 105, 107) has given rise to empiric treatment with a host of other agents, including amoxicillin with or without probenecid, doxycycline, minocycline, and cephalosporins. Meningitis and arthritis have generally been treated with intravenous antibiotics; penicillin (103, 108–111) and ceftriaxone (110, 111) have been used most frequently, cefotaxime (112, 113) less frequently, and chloramphenicol (41) rarely.

The authors' approach to treatment is outlined in Table 5, but it is by no means the last word. Neither the drugs of choice for Lyme disease, nor the optimal route of administration and duration of treatment, nor indications for retreatment have been clearly defined. Patients treated with tetracyclines should be warned about photosensitivity rashes (Fig. 6) and instructed to avoid the sun or use sunscreen. Tetracyclines are contraindicated in pregnant women and in children less than 8 years old.

Because of the risk to the fetus related to spirochetemia, and because of at least one anecdotal report of failure of oral therapy to protect the fetus from infection in a pregnant woman with erythema migrans (75), it is our practice to treat

TABLE 4
Antibiotic Regimens Useful for Treatment of Lyme Disease

Oral Regimens for Adults*
Preferred
Tetracycline 500mg QID†
Doxycycline 100mg BID or TID†
Phenoxymethyl penicillin 500mg QID
Amoxicillin 500mg TID
Alternative
Erythromycin 500mg QID
Cefuroxime 500mg BID
Parenteral Regimens for Adults*
Ceftriaxone 2gms IV QD
Penicillin G 3–4 × 10^6 units IV Q4H
Cefotaxime 2gms IV QID

* Children can be treated using the same antibiotics in maximal pediatric doses.

† Not for children under 8 years old or for pregnant or lactating women.

pregnant women who have active Lyme disease with intravenous penicillin or ceftriaxone. The antibiotic of choice in a highly penicillin-allergic child or pregnant woman has not been determined. Erythromycin may be used but response to this drug has not been optimal (104, 105).

All patients should be warned of the potential for a Jarisch-Herxheimer reaction, a transient worsening in the first 24–48 hours of clinical symptoms (fever, arthralgias, malaise, headache, fatigue) which occurs in about 15% of patients (105). This need only be treated symptomatically with aspirin or nonsteroidal antiinflammatory agents. These medications also may be quite useful in symptomatic relief at other times during and following antibiotic treatment. Steroids have not been clearly shown to be helpful in Lyme disease and may possibly be associated with a worse outcome (110).

Prognosis

Patients treated early in the course of illness have an excellent long-term prognosis.

Post-Lyme Syndrome. However, as many as one-half of patients will continue to have a variety of complaints of uncertain etiology for months (105), including fatigue, arthralgias, myalgias, malaise, and difficulty concentrating ("post-Lyme syndrome"). Since these may occur even after intravenous treatment, there is reason to suspect that some symptoms may be related to the body's immune response to the spirochete rather than to direct effects of the viable organism. The persistence of the post-Lyme syndrome is highly frustrating for both the patient and the physician. Antiinflammatory agents, reassurance, and sometimes physical therapy may be all that is required.

Patients should be monitored for their *clinical* response to therapy. Antibody titer has not been correlated with severity of illness or prognosis. There is no serologic "test of cure" analogous to the VDRL for syphilis by which to gauge the success of therapy in Lyme disease patients. The persistence of elevated titers of antibody to *B. burgdorferi* or increased lymphocyte response to *Borrelia* antigen months after therapy is *not* an indication to re-treat a patient who is otherwise doing well.

Erythema Migrans. Erythema migrans resolves rapidly with appropriate antibiotics, usually within a few days. Untreated lesions may take several weeks to resolve (average 3 weeks), and may recur (13, 14, 22).

Cardiac Disease. Most patients with cardiac disease recover completely with antibiotic therapy, although temporary pacemakers may be required. On occasion, however, atrioventricular block may persist (28). At least one fatality has been reported in an untreated patient with both Lyme disease and babesiosis, who had spirochetes visualized in the myocardium at autopsy (27).

Neurologic Disease. Patients with facial nerve palsy typically do not have symptom resolution for about 3–4 weeks, whether or not they are treated with antibiotics (49), but therapy is indicated to prevent other complications of Lyme disease. Patients with meningitis who are treated with intravenous antibiotics improve significantly more quickly than untreated patients based on historical controls (108). Long-term studies have not determined the overall prognosis for patients with other neurologic complications. Failures of high-dose penicillin (41, 111, 114) and ceftriaxone (109, 114) have been reported.

Steroid treatment has not been convincingly shown to have a role in neuroborreliosis. Preliminary findings from a randomized placebo-controlled trial failed to show a clear benefit from the addition of steroids to penicillin in the treatment of patients with radiculitis (115).

Arthritis. Although in children Lyme arthritis generally responds well to antibiotic therapy (116, 117) and may resolve eventually even without treatment (118), adults appear to fare less well. As many as 50% of adult patients with arthritis fail to respond to a single course of high-dose intravenous penicillin (106). Some of these patients will respond to intravenous ceftriaxone (111). Oral antibiotics also have been successfully used in Lyme arthritis (116, 117, 119), and it

TABLE 5
Authors' Approach to Treatment of Lyme Disease

Manifestation	Treatment* Oral vs Parenteral	Preferred duration in days	Comments
Erythema migrans	Oral	10–21	
Flulike illness thought to be Lyme	Oral	10–21	
Facial nerve palsy	Oral	10–21	
Meningitis	Parenteral	10–14	
Encephalitis	Parenteral	10–14	
Radiculopathy	Parenteral	10–14	Oral therapy effective anecdotally
Heart block			
PR <.3 sec	Oral	10–21	
Advanced, PR ⩾.3 sec or 2° or 3°	Parenteral	10–14	Temporary pacemaker to be considered
Arthritis	Oral	30	If oral therapy fails, give parenteral Rx 10–14 days
Post-Lyme syndrome†	Oral†	10–21†	Reassurance & nonsteroidal antiinflammatory drugs are a major part of therapeutic approach†
Asymptomatic seropositive‡ (never treated)	Oral‡	14–30‡	Observation an alternative‡
Tick bite in endemic area			
Asymptomatic	Observation only		
In pregnant woman	Oral	10–14	Do not give tetracyclines
Lyme disease in pregnant woman	Parenteral	10–14	Do not give tetracyclines

* Suggested treatment regimens are found in Table 4.
† Many of the most severely affected patients have been treated by a course of antibiotics, although its value is unproven.
‡ Whether to administer antibiotics has not been established.

would be reasonable to try a course of oral antibiotics first, reserving intravenous therapy for those who do not respond adequately. Of interest, nonresponders to an oral antibiotic regimen often do not improve even with intravenous therapy (119), possibly due to a genetic predisposition to more severe illness (61, 62).

Selected patients who fail to respond to antibiotics may benefit from synovectomy (120). Although nonsteroidal antiinflammatory agents appear to have an adjunctive role in treating Lyme arthritis, the use of intraarticular steroids is controversial (23, 110).

Other Symptoms. A certain small group of patients who have a variety of symptoms (flulike, constitutive, neurologic, rheumatologic) appear to be refractory even to high-dose intravenous antibiotics. The reason for this, and the appropriate management of these patients, are unclear, as noted above.

Prevention

The most important means of preventing Lyme disease is to avoid tick bites (see ruled box). If a tick bite does occur, removing the tick (with fine-tipped forceps) as soon as possible may interrupt spirochetal transmission. Soap and water should be applied to all bites.

There are not yet enough data to warrant treating asymptomatic tick bite victims with prophylactic antibiotics. Indeed, the cost and risks of antibiotics (rash, diarrhea, nausea) may be greater than the potential benefits, since most *Ixodes* bites appear not to result in Lyme disease (16–18). However, because of the possibility of transplacental transmission of Lyme disease and the potential for serious sequelae, it is our prac-

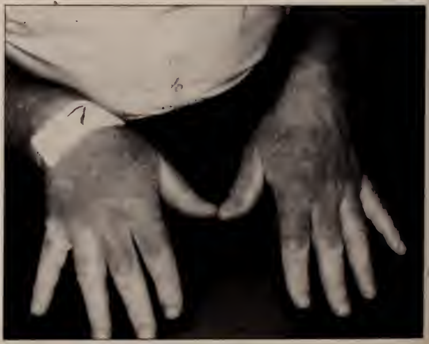

Fig. 6. Photosensitivity rash on hands of patient receiving doxycycline for treatment of erythema migrans.

tice to treat pregnant women bitten by *Ixodes* prophylactically with oral penicillin.

The role of pesticides and deer population control in preventing Lyme disease require further study. No effective vaccine exists at present.

Questions for Research

Diagnosis. Better diagnostic tests are needed to give reliable and expedient results at affordable prices. Antigen testing, improved culture techniques, polymerase chain reaction, and lymphocyte stimulation testing are currently being studied.

Treatment. Controlled prospective studies are essential to determine the optimal antibiotic regimen, including duration and route (oral vs. intravenous), for each manifestation of Lyme disease. A simple laboratory "test of cure" to gauge success of therapy would be immensely helpful in patient management. Standardized in vitro antibiotic susceptibility testing will be useful in the development of improved treatment regimens.

Transmission of Illness and Prevention. Research into effective methods for controlling the proliferation and spread of *Ixodes* populations are badly needed. For example, the importance of birds and small mammals (other than the white-footed mouse) in spreading the tick to new areas is unclear. Factors responsible for development of Lyme disease after a tick bite, and whether illness can be readily prevented with prophylactic antibiotics require further study. The role of various arms of the immune system in both host defense against spirochetes, and the development and persistence of illness, needs further elucidation.

Better preventive strategies must be developed. A cost-benefit analysis must be established to determine whether limiting the deer, mouse, or tick populations are feasible means of preventing illness. Finally, understanding the molecular and immunologic aspects of host response to *B. burgdorferi* may enable development of an effective vaccine. It is sobering to remember, however, that a vaccine against syphilis is not yet on the horizon, almost a century after the discovery of its etiologic spirochete.

Acknowledgments

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Recommendations for Preventing Tick Bites

- Wear light-colored clothing so ticks can be seen more easily.
- Tuck shirts into pants and pants into socks.
- Wear shoes which are not open-toed.
- Use an insect repellent containing N,N-diethyl-m-toluamide (DEET) or permethrin (the latter is not available in New York State)
- Check yourself and others for ticks daily under good lighting.
- Wash clothes after being in a tick-infested area.
- Check frequently for ticks on pets.

Removing the Tick

If a bite occurs, the tick should be removed immediately (preferably with forceps), and the area cleaned with soap and water. Removing ticks with bare hands, or attempting to "burn" the tick, or "suffocate" it with oil or petroleum jelly, is NOT recommended.

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Anesthesia in the Presence of Complete Fetal Atrioventricular Heart Block:

An Anesthetics Dilemma

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Neonatal lupus erythematosus is an uncommon disorder primarily affecting infants born to mothers with systemic lupus erythematosus (SLE). Two common clinical manifestations are transient cutaneous lesions that resolve during infancy and the more serious phenomenon of congenital atrioventricular block (1). In this case report we review this disorder and discuss the anesthetic management of an emergency cesarean section in the presence of known fetal atrioventricular block.

Case Report

The patient was a 25-year-old, 60-kg primagravida who had a five-year history of systemic lupus erythematosus. She had been asymptomatic for two years and had received no prednisone during this time. Except for SLE, her medical history was normal. There were no allergies and no recent medications. Routine laboratory studies were normal. At 41 weeks gestation an oxytocin challenge test was performed. Prior to the test the fetal heart rate was 80/min. During the stress test, fetal heart rate dropped to 40/min. A fetal electrocardiogram showed complete heart block.

A cesarean section was scheduled. General anesthesia was induced, after preoxygenation, with sodium thiopental 180 mg and succinylcholine 80 mg, both intravenous. Following endotracheal intubation, anesthesia was maintained with oxygen 6 L/min and enflurane 1.3% until delivery of the baby.

A male, weight 3450 g, was delivered 10 minutes after induction of anesthesia. Respiration was poor and endotracheal intubation was performed for tracheal suctioning and assisted ventilation. The Apgar score at 1 minute was 7 (1 color 1 respiration 1 heart rate) and 9 at 5 minutes (1 heart rate). The child was taken to the neonatal intensive care unit, where an EKG showed complete heart block with an atrial rate of 170/minute and ventricular rate of 55/minute. There were frequent ventricular premature beats at 10/minute. A 2-D echocardiogram demonstrated a large left ventricle with poor ventricular contraction. Other significant physical findings were a heart rate of 50/minute, a II/VI systolic murmur best heard at the left sternal border, and respiratory rate of 50–70 minute. Blood pressure was 66/28 mmHg. There was no evidence of congestive heart failure.

Oxygen by ventimask with an FiO2 of 0.25 was given to maintain PaO2 at 95 mmHg. On day 2, a transvenous ventricular pacemaker (rate 130/minute) was inserted into the right saphenous vein. The pacemaker did not capture continuously. An attempt to increase the ventricular rate with an isoproterenol infusion at 0.1 mcg/kg per minute was unsuccessful. Voltage was increased several times over the next few days to allow continuous capturing. On day 9, an epicardial permanent pacemaker was inserted and set at rate of 122/minute. Oxygen therapy was discontinued on the 11th day after birth. The baby was discharged home on the 17th day.

Discussion

The incidence of congenital heart block associated with neonatal lupus erythematosus is reported to be approximately 1 in 20,000 births (2). Other abnormalities include thrombocytopenia (3), autoimmune hemolytic anemia (4), and increased liver enzyme concentrations (5). Watson

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et al (6) have reported a close association between neonatal lupus erythematosus and the presence of SS-A (Ro) and SS-B (La) antibodies in the mother and affected child. Ro and La antibodies are RNA protein complexes related to messenger, nucleolar, or transfer RNA. Ribonucleoprotein particles in both the cell nucleus and the cytoplasm are attacked by the antibody system (7). Fetal cardiac Ro antigen levels are comparable to adult values at 18 to 23 weeks (8). Cardiac lesions are present at birth. The cause of these cardiac defects is thought to be inflammatory myocarditis. There is replacement of the A-V nodal tissue by elastic, fibrous, or adipose tissue (9). Buyon et al (10) have used maternal plasmapheresis and dexamethasone in an attempt at therapy when fetal myocarditis and heart block were found at 24 weeks gestation. They describe a child born at 31 weeks with heart block, despite a fall in La antibody titers. It is possible that this treatment might have been more effective if performed earlier.

Congenital complete heart block is characterized by an absence of impulse conduction between the atria and the ventricles. Heart rate is usually below 80 beats/min compared to the normal average infant-fetal rate of 130/min. Prenatally, the diagnosis of congenital heart block is suspected if the fetal heart rate is below 100/min in the absence of a cause for fetal distress. The differential diagnosis of fetal bradycardia is essential for subsequent management of pregnancy. External fetal monitoring with either a Doppler monitor or a phonocardiogram has limitations. The Doppler may give falsely high fetal heart rates by recording atrial rather than ventricular rates.

The recent development of fetal echocardiography has provided a more efficient diagnostic method. Two-dimensional echocardiography is useful for anatomy and the M-mode is particularly useful if the M-mode cursor is positioned so that it intersects both an atrial wall and a ventricular wall, recording the simultaneous motion of both chambers (11). In complete heart block, M-mode tracings of the fetal echocardiogram show a ventricular contraction rate at a much slower rate, 50–100 beats per minute, than those of the atrium, approximately 140 beats per minute and totally dissociated from atrial contraction. Doppler flow velocity tracings across valvular orifices are similarly disparate.

Echocardiography also provides evidence that the heart is structurally normal. This helps differentiate heart block due to connective tissue disease from complete heart block with structural heart disease, which has a poorer prognosis. Serial fetal left ventricular echocardiograms may give early warning of the onset of left ventricular dilatation and congestive heart failure.

Occasionally fetal hydrops develops (12). The prognosis depends on maturity, as immediate delivery is indicated. Transabdominal pacing via chest-wall puncture has been attempted when prematurity prevented delivery (13). Although technically feasible, it has not been successful. There are problems of maintaining the wire in place once the fetus regains its activity. The authors suggest that a transumbilical vein pacing wire might be more efficient.

In late pregnancy, a fetal scalp-tissue pH estimation is helpful in determining fetal metabolic status. A normal pH obviates the need for immediate intervention. A fetal electrocardiogram is also helpful in the diagnosis at this stage. The P waves are seen to occur at a higher rate than the QRS complexes. When the block is proximal to the bundle of His, QRS complexes are narrow (0.1 sec) and of abnormal configuration. With an increasingly distal block, there are wider QRS complexes and a slower heart rate.

Anesthetic Management

Anesthetic management of patients with congenital heart block can be hazardous. Asystole is an ever-present risk. Careful selection of anesthetic agents is needed to avoid further depression of AV conduction. When complete fetal heart block is present, placental transfer and fetal pharmacokinetics must be taken into account.

Either general or regional anesthesia can be used for cesarean section. Drugs given to the mother cross the placenta and enter the fetal circulation almost entirely by passive diffusion. The maternal concentration of the drug, the uterine and umbilical blood flow, and physiochemical properties of the drug determine placental transfer. Physiochemical properties that allow rapid transfer are high lipid solubility, low ionization, low molecular weight, and low protein binding. Following placental transfer, the effects on the fetus depend on the drug uptake, distribution, metabolism, and elimination. Most anesthetic agents have high lipid solubility, are partially nonionized at pH 7.4, have molecular weights of less than 500, and are at least partially nonprotein-bound in maternal blood. An exception is quaternary ammonium compounds such as the muscle relaxants.

These placental transference factors and the effects of drugs on the fetal heart are important when we provide anesthesia for cesarean section in the presence of complete fetal heart block. Drugs that depress SA nodal tissue are only important if the block is partial or intermittent. However, any drug which depresses cardiac impulse formation in the AV node, its bundle, or ventricular muscle may produce asystole in these patients.

Barbiturates cross the placenta rapidly but fetal concentrations are not high if maternal doses are less than 4 mg/kg intravenously (14). Ketamine has also been used successfully as an induction agent for cesarean section (15). Inhalational anesthetics cross the placenta rapidly. Low-dose halothane, enflurane, and isoflurane do not appear to have major depressant effects on the fetus. Neuromuscular blocking agents such as quaternary ammonia compounds are fully ionized hydrophylic compounds that cross the placenta slowly. They have been used safely during cesarean section without fetal neuromuscular blockade (16–19). The agents described above would provide safe anesthesia for delivery of a fetus with congenital complete heart block.

Narcotic analgesics are not used clinically as a part of the anesthetic technique prior to delivery of the infant.

The commonly used local anesthetic agents for regional anesthesia in obstetrics are lidocaine, bupivacaine, and 2-chloroprocaine. Deceleration of fetal heart rate with dysrhythmias has been observed during epidural anesthesia when chloroprocaine or bupivacaine is used (20). These dysrhythmias were not associated with maternal hypotension, abnormal uterine activity, or abnormally high levels of local anesthetic in the mother or fetus. Nonetheless, bradycardia, heart block, and ventricular tachycardia have been reported in infants following intravenous lidocaine injection (21). Bupivacaine is reported to be more cardiotoxic than other local anesthetic agents (22). The newborn has an immature cardiac conductive system, and sympathetic innervation is also not well developed. Epinephrine levels are low. These newborns may be more susceptible to lidocaine toxicity.

Although regional anesthesia is used for most cesarean sections, we believe inhalational anesthesia to be the technique of choice for cesarean section in mothers with a fetus who has congenital complete heart block because this technique causes less depression of the immature fetal cardiac conductive system.

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Serum Creatinine in Patients with Spinal Cord Injury

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Abstract

In a group of 18 male patients with spinal cord injury, we found serum creatinine to be within normal limits or only minimally elevated despite significant reduction in creatinine clearance. In 8 control subjects with serum creatinine between 1.0 and 1.5 mg/dL (88.4 and 132.6 μmol/L), the measured creatinine clearance was 66.4 ± 28.2 mL/min. In contrast, in the 5 patients with spinal cord injury whose serum creatinine was in the same range, the measured creatinine clearance was only 31.0 ± 19 mL/min. Urinary creatinine excretion was lower in patients with spinal cord injury than in the 18 male controls (653 mg/24 hr vs. 1505 mg/24 hr). The decreased urinary creatinine could not be explained by differences in age, sex, or body weight. We calculated the relationship of creatinine clearance (C_{cr}) and serum creatinine (S_{cr}) in patients with spinal cord injury to be given by the equation

$$C_{cr}\ (\text{mL/min}) = 45/S_{cr}\ (\text{mg/dL}),\ r = 0.73.$$

We recommend timed urine collections for creatinine to estimate creatinine clearance accurately for clinical evaluation of patients with spinal cord injury.

Patients with spinal cord injury (SCI) are afflicted with a variety of renal diseases, such as nephrolithiasis, urinary tract infections, and amyloidosis (1–5). Many diagnostic and therapeutic decisions are influenced by the assessment of renal function in these patients, including the adjustment of maintenance doses of drugs excreted via the kidney, the evaluation of symptoms of uremia, and the decision to initiate dialysis. Therefore, it is of obvious importance to assess the glomerular filtration rate in these patients.

In a group of patients with SCI we noted that serum creatinine (S_{cr}) was elevated either minimally or not at all, despite significant decrease in creatinine clearance. Thus, the serum creatinine level appeared to underestimate the degree of renal function in these patients. This investigation was undertaken to better define the relationship between renal function (C_{cr}) and serum creatinine in patients with spinal cord injury.

Methods

The control group consisted of 18 male patients without SCI who had a variety of renal diseases. The study group consisted of 18 male patients with long-standing SCI with paraplegia or quadraplegia and a range of serum creatinine values. The average duration of SCI was 7.3 years (range, 2 to 23 years).

All measurements were performed within a six-week period at the Veterans Administration Medical Center, Bronx, NY. Creatinine was measured by the Auto-Analyzer. Glomerular filtration rate (GFR) was derived from serum creatinine by one of three formulas.

Edwards and Whyte (6):

$$\text{GFR (mL/min)} = 94/S_{cr}\ (\text{mg/dL})$$

Jelliffe (7):

$$\text{GFR (mL/min)} = \{98 - 16\ ([\text{age} - 20]/20)\}/S_{cr}\ (\text{mg/dL})$$

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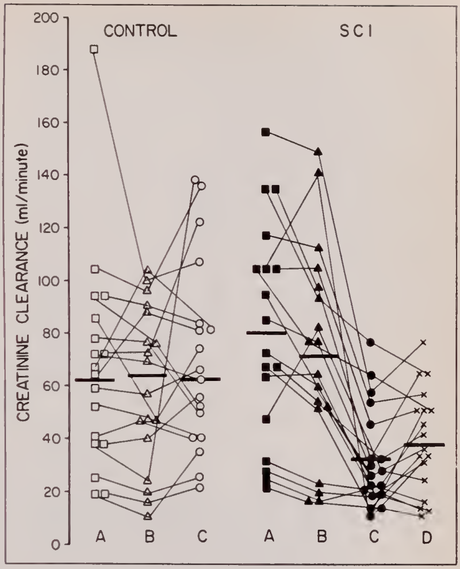

Fig. 1. Comparison of calculated and measured creatinine clearance in 18 male control subjects (open symbols, left) and in 18 male spinal cord injury (SCI) patients (closed symbols, right). A, C_{cr} calculated by formula of Edwards & Whyte (6). B, C_{cr} calculated by formula of Cockcroft and Gault (8). C, measured 24-hr creatinine clearance. D, SCI patients, C_{cr} calculated by equation derived in this paper. In SCI patients, formulas used in clinical practice (6, 8) overestimate C_{cr}.

Cockcroft and Gault (8):

$$\text{GFR (mL/min)} = (140 - \text{age in years})(\text{wt in kg}) / (72 \times S_{cr} \text{ in mg/dL})$$

The values of S_{cr} represent a steady-state value, since S_{cr} did not change during the period of measurement.

Measured creatinine clearance was derived from the serum creatinine and 24-hr urine creatinine levels by using the standard equation. All but two SCI patients had indwelling urinary catheters, and the creatinine clearance values were measured from these accurately collected samples. In 9 of 18 controls and 11 of 18 SCI patients, urine collection was performed at least twice, and the average 24-hr urine creatinine value was used for calculating creatinine clearance. All urine collections were personally supervised by one of us; the difference in two values for 24-hr urine creatinine excretion in the same patient was 15% or less. None of the controls or SCI patients was receiving drugs which interfere with measurement of creatinine by the Auto-Analyzer or which would influence GFR. To exclude the uncommon possibility of creatinine consumption by bacterial overgrowth in SCI patients (9), we examined the urine creatinine concentration over time in 15 of 18 SCI patients. Urine creatinine concentration was stable over time in all SCI patients so tested.

The significance between means ($p < .05$) was calculated by the unpaired *t* test.

Results

There was no significant difference in mean age, weight, and serum creatinine between the control subjects and SCI patients (Table). The 24-hr urinary creatinine excretion was significantly lower in SCI patients than in controls. Creatinine excretion corrected for weight was also lower in the SCI than in the control group.

Creatinine clearance was calculated by one of three formulas. The first employs only serum creatinine (6), the second takes age into account (7), and the third corrects for age and for weight as well (8). In control subjects the calculated values for C_{cr} were similar by all three methods and corresponded closely to the measured C_{cr} of 68.3 mL/min. Estimated creatinine clearance by two of these formulas (Fig. 1, A and B) compared with the measured 24-hr creatinine clearance (Fig. 1, C) supports the same conclusion.

In SCI patients the calculated C_{cr} by the three methods agreed closely with each other (Table). However, the measured mean C_{cr} of 32 mL/min (Fig. 1, C) was markedly lower than the calculated mean C_{cr} values of 61–84 mL/min (Table; Fig. 1, A and B).

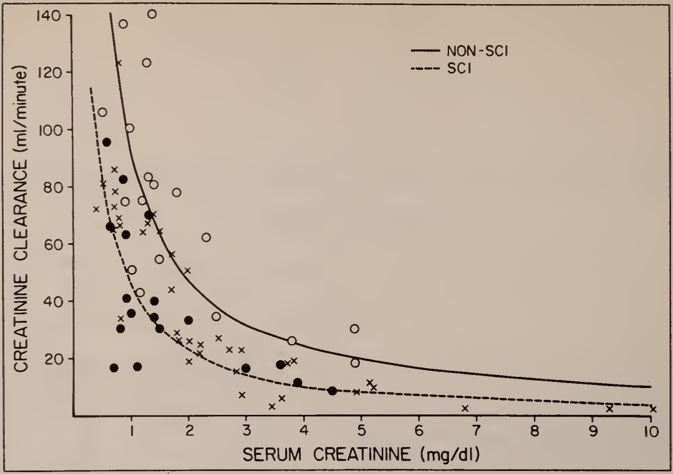

Fig. 2. Relationship between measured creatinine clearance and serum creatinine in 18 male control subjects (open circles), 18 male subjects with longstanding spinal cord injury (SCI) (closed circles), and 19 patients from a paraplegic unit in Great Britain (crosses) with longstanding SCI studied and reported on many times (refs. 1–3) with different S_{cr} and C_{cr} values, yielding 38 data points. Solid curved line depicts relationship between two parameters in normal subjects as given by formula of Edwards & Whyte, $C_{cr} = 94/S_{cr}$ (mg/dL) (6). Broken line depicts relationship between these parameters in patients with SCI (C_{cr} in mL/min $= 45/S_{cr}$ in mg/dL, $r = 0.73$), using equation derived in this paper.

Examining the relationship between serum creatinine and C_{cr} in 18 control subjects, 18 SCI patients, and 19 patients with longstanding SCI from a paraplegic unit in Great Britain (1, 2, 3) showed that for any given level of serum creatinine, measured C_{cr} was lower in SCI patients than in controls. The C_{cr} estimated from serum creatinine by the method of Edwards and Whyte (6) corresponded quite well with the measured 24-hr creatinine clearance in control subjects, but overestimated the C_{cr} in SCI subjects by a considerable margin.

TABLE

Clinical and Biochemical Profile of 18 Male Controls and 18 Male Patients with Spinal Cord Injury (SCI)
(Means ± SD)

	Control	SCI	*P*
Age (years)	58 ± 9	55 ± 10	NS
Weight (kg)	75 ± 16	71 ± 23	NS
Serum creatinine			
(mg/dL)	2.0 ± 1.3	1.7 ± 1.2	NS
(μmol/L)	176.8 ± 114.9	150.3 ± 160	NS
Urinary creatinine			
(mg/24 hr)	1505 ± 562	653 ± 290	<.001
by weight (mg/kg)	20.8 ± 8.8	9.7 ± 4.6	<.001
Calculated C_{cr} (mL/min)			
Edwards & Whyte	67.4 ± 38.8	80.8 ± 40.0	NS
Jelliffe	48 ± 26	61.0 ± 30.4	NS
Cockcroft & Gault	59.8 ± 29.2	71.9 ± 38.9	NS
Measured C_{cr} (mL/min)	68.3 ± 35.6†	32.3 ± 18.6*	<.001*

C_{cr}, creatinine clearance; NS, not significant compared to controls.
* $P < .001$ compared to C_{cr} calculated by three methods.
† NS compared to C_{cr} calculated by three methods.

New Equation for Relationship between Serum Creatinine Level and Creatinine Clearance. To obtain a relationship between serum creatinine and C_{cr} in SCI patients, we plotted C_{cr} versus the reciprocal of S_{cr} in 18 SCI patients studied here and in other SCI patients reported in the literature. Since the slopes and the intercepts of the line correlating C_{cr} with $1/S_{cr}$ was not different for the 18 SCI patients studied by us and for other SCI patients reported in the literature, we pooled the data and derived an equation correlating C_{cr} with serum creatinine.

C_{cr} in SCI subjects was given by the formula

$$C_{cr}(\text{mL/min}) = 8.2 + 38/S_{cr}(\text{md/dL}), \quad r = 0.75. \tag{1}$$

Thus, the equation gave a reasonable approximation of the C_{cr} from serum creatinine in SCI patients. Attempts to improve the fit by incorporating age and weight into this equation failed; the correlation coefficient did not improve further. To simplify equation (1) in SCI patients, we forced the line through the origin. This yielded the equation:

$$C_{cr} = 45/S_{cr}\ (\text{mg/dL}),\ r = 0.73. \tag{2}$$

This relationship is shown by the broken line in Fig. 2.

In SCI patients, the C_{cr} calculated from plasma creatinine by our equation (Fig. 1, D) agreed closely with the measured C_{cr} (Fig. 1, C).

Discussion

The assessment of glomerular filtration rate (GFR) may be performed by a variety of different techniques. Although accurate, the renal clearance of inulin or radiolabelled compounds such as iothalamate are cumbersome, expensive, and not widely available for routine clinical estimation of GFR. Therefore, routine clinical evaluation of GFR has been performed by measurement of endogenous creatinine clearance (C_{cr}) or that of steady-state serum creatinine (S_{cr}).

The difficulties associated with measurement of C_{cr}, such as the need for reliable urine collections, have led to the development of various formulas to estimate the creatinine clearance from serum creatinine (6–8). Our results confirm those of earlier workers and suggest that in subjects without spinal cord injury, the 24-hr measured creatinine clearance agrees well with the value for C_{cr} calculated by these formulas (Table, Fig. 1). In contrast, in SCI patients, these formulas failed to predict C_{cr} accurately from serum creatinine (Table; Fig. 1, right panel). The average serum creatinine in SCI patients of 1.7 mg/dL was associated with a marked decline in average creatinine clearance (32 mL/min, Table). For any given level of serum creatinine, C_{cr} was lower in SCI patients than in controls (Fig. 2). In 8 control subjects with serum creatinine between 1.0 and 1.5 mg/dL, the measured C_{cr} was 66.4 ± 28.2 mL/min. In contrast, in the 5 SCI patients with S_{cr} in the same range, the measured C_{cr} was 31.0 ± 19.7 mL/min. Thus in SCI patients with marked reduction in creatinine clearance, the serum creatinine level was within the normal range or only mildly elevated.

Creatinine clearance has been reported to overestimate the clearance of inulin or radiolabelled DTPA (10–13). Recently, it was shown that the ratio of creatinine clearance to inulin clearance exceeded unity, but remained constant over a wide range of inulin clearances (14). Insofar as the creatinine clearance overestimates inulin clearance, a low creatinine clearance in SCI patients will represent an even greater impairment of glomerular filtration rate.

It is apparent (Table) that 24-hr urine creatinine excretion was markedly lower in SCI patients, and this datum accounts for the discrepancy between the calculated and measured values of C_{cr}. We have reported previously that in some SCI patients, urinary bacteria consume creatinine over a period of time (9), but in the present report, that possibility was excluded by the finding that urinary creatinine was stable over time. A decrease in urinary creatinine may occur with increasing age (15), but this did not explain the lower creatinine excretion in SCI patients, because the mean age was not different in the control and SCI groups. Similarly, the lower creatinine excretion in SCI patients was not a consequence of lower body weight, because urinary creatinine per kilogram of weight was also markedly lower in SCI patients as compared to controls (9.7 ± 4.6 mg/kg vs. 20.8 ± 8.8 mg/kg). Malnutrition or diminished protein intake may result in decreased creatinine output, but there was no clinical evidence of malnutrition or decreased protein intake in our SCI patients.

The lower creatinine excretion in SCI patients is most likely secondary to decreased creatinine production from atrophic or inactive muscles secondary to spinal cord injury, but enhanced degradation of creatinine in the gut or enhanced extrarenal excretion as seen in chronic renal failure (16) may also explain the finding in SCI patients.

In summary, patients with spinal cord injury have a deceptively low level of serum creatinine despite considerable decrease in creatinine clearance. The extent to which patients immobilized by other neurologic diseases also exhibit this finding has not been established. In most clinical situations, creatinine clearance can be estimated with reasonable accuracy using formulas which take age, sex, and weight into account (6, 8). However, when the patient has a spinal cord injury, serious underestimation of C_{cr} will occur with this approach. Timed urine collections for creatinine measurement are necessary to evaluate creatinine clearance clinically in those patients who have spinal cord injuries.

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Hepatocellular Carcinoma associated with Autoimmune Chronic Active Hepatitis

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Abstract

Primary hepatocellular carcinoma, one of the most common malignancies in the world, develops in chronic liver diseases of different etiologies. Hepatitis B and non-A, non-B infections, alcoholic cirrhosis, hemochromatosis, contamination with aflatoxins, and oral contraceptives are just a few of the conditions that have been associated with this carcinoma. To our knowledge, few cases of autoimmune chronic active hepatitis and hepatocellular carcinoma have been reported in the literature. We describe a patient who developed hepatocellular carcinoma 21 years after the onset of the autoimmune hepatitis.

HEPATOCELLUAR carcinoma, the most common fatal malignancy worldwide, is a relatively uncommon neoplasm in the United States (1, 2). Almost all cases in areas with endemic hepatitis B infection are associated with the virus (2, 3). In other parts of the world, other factors have been incriminated, particularly alcoholism (4); aflatoxins (5, 6); exposure to sex steroids, Thorotrast, and vinyl chloride; and metabolic abnormalities (7). Hepatocellular carcinoma has been associated, but rarely, with the autoimmune liver diseases primary biliary cirrhosis (8, 9) and autoimmune chronic active hepatitis (10–17). We report the case of a patient with autoimmune hepatitis and hepatocellular carcinoma.

Case Report

A 50-year-old white woman went initially to another hospital in July 1967 with a two-month history of fatigue, anorexia, dark urine, and jaundice. She was treated conservatively with supportive care for presumed acute hepatitis and discharged feeling better. Two months later, she was readmitted with similar symptoms. A liver biopsy performed at the time was interpreted as acute hepatitis. Therapy of 60 mg/day of prednisone was begun and was gradually tapered to a maintenance dose of 10 mg/day. She remained stable until January 1970, when she had a flare-up of her initial symptoms after the prednisone was decreased to 5 mg/day. The prednisone was increased to 15 mg/day, and she remained on that dose until July 1977, when another dose reduction was attempted. She again had a flareup of symptoms 4 months later, and was treated with phenobarbital 300 mg/day. Initially she reported some improvement but still complained of severe fatigue and anorexia. In June 1978, phenobarbital was discontinued and therapy with prednisone 10 mg and azathioprine 50 mg/day was instituted. Her symptoms improved and she was again tapered off all medication by December 1980.

In January 1981, she came to The Mount Sinai Hospital with massive upper gastrointestinal bleeding from ruptured esophageal varices, and endoscopic sclerotherapy was begun. The liver biopsy specimen from 1967 was reviewed. It

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showed enlargement of the portal tracts due to dense lymphocytic infiltrate and mild increase in fibrous tissue, with piecemeal necrosis and areas of collapse. Spotty necrosis and lymphocytic infiltration were seen diffusely throughout the lobules. The clinical features, the laboratory values, and the liver biopsy findings with the areas of collapse were consistent with chronic active hepatitis of autoimmune type. In November 1983 she developed ascites and peripheral edema, which was managed with sodium and water restriction and diuretics. She reported no intake of alcohol.

Physical examination in February 1988 revealed a well-developed, well-nourished, jaundiced woman. The liver was enlarged and irregularly shaped, extending 6 cm below the right costal margin. The spleen was 4 cm below the left costal margin. She had spider angiomata on her chest and shoulders. Ascites and peripheral edema were not present.

Pertinent laboratory data included albumin of 33 g/L (normal, 32–45 g/L), globulins 48 g/L (normal 23–35 g/L), gamma globulin 22.2 g/L (normal 5–16 g/L), total bilirubin 38.7 μmol/L (normal, 2–18 μmol/L), alkaline phosphatase 631 U/L (normal 30–115 U/L), gamma glutamyl transferase 91 U/L (normal 2–39 U/L), alanine aminotransferase 137 U/L (normal 2–50 U/L), aspartate aminotransferase 186 U/L (normal 2–40 U/L). Test results for hepatitis B surface antigen, hepatitis Be antigen, anti-hepatitis B core, and anti-hepatitis B surface were negative, as were tests for antinuclear and antimitochondrial antibodies; however, results were positive for anti-smooth-muscle antibodies, with titers above 1:320. Alpha-fetoprotein was 237 IU/mL (normal <2.5 IU/mL).

Ultrasound showed large masses occupying most of the right lobe of the liver and the medial segment of the left lobe. A liver biopsy was performed and a diagnosis of hepatocellular carcinoma was made.

Combination chemotherapy was initiated, and partial response was indicated by a decrease in serum alpha-fetoprotein level and shrinkage of the tumor masses on ultrasound. She subsequently developed intractable ascites resistant to diuretics which necessitated placement of a Denver peritoneo-atrial shunt. Eleven months after the diagnosis of hepatocellular carcinoma was made, she died. An autopsy was performed.

Liver Biopsy Findings. The lobular architecture was disturbed. Hepatocytes were arranged into columns 2 to 5 cells thick (Fig. 1). In areas the columns were separated from each other by thin strands of fibrous tissue. Minute droplets of canalicular bile were found occasionally within the trabeculae. The number of vascular channels was increased (Fig. 2); some had arterial walls. Only mild pleiomorphism of the nuclei was noted. Mitotic figures were rare. The tumor cells had eosinophilic cytoplasm resembling normal hepatocytes. Clusters of cells with steatosis and Mallory's hyalin in their cytoplasm were seen. Thin strands of lamellar or hyalinized fibrosis extended between the neoplastic hepatocytes (Fig. 3). In areas these fibrotic strands coalesced and formed broad regions of fibrosis. Mononuclear cells, mainly plasma cells, infiltrated the tumor (Figs. 1, 4). Nontumorous parenchyma was not recognizable.

Autopsy Findings. At autopsy, the patient was cachectic and deeply jaundiced. The liver weighed 1050 g, of which 50%–60% was necrotic tumor. Tumor nodules were present in both lobes of the liver. No extrahepatic metastases were noted. The tumor had the same histologic features as the biopsy specimen. The nontumorous liver revealed inactive cirrhosis with minimal inflammatory infiltrate and severe cholestasis.

Discussion

Hepatocellular carcinoma is one of the most common fatal malignant neoplasms worldwide (1, 2). It is rare in many parts of the world, such as North and South America, northern and central Europe, and Australia, where it constitutes only about 0.5%–2% of all cancers. However, in densely populated regions such as sub-Saharan Africa, Southeast Asia, China, Japan, and Oceania, its incidence can be as high as 20%–40% of all cancers.

These striking geographical variations in incidence strongly suggest that environmental factors contribute to hepatocarcinogenesis. Aflatoxin has long been incriminated as a possible environmental factor, particularly in hot humid climates (5, 6). In experimental animals, including primates, aflatoxin per unit weight has been the most potent carcinogen known. Nevertheless, the evidence that aflatoxin causes human hepatocellular carcinoma remains circumstantial.

Other factors commonly associated with this carcinoma are alcohol abuse (4, 7) and hepatitis B virus (HBV) (1–3). In Western countries, these two factors are found in about two-thirds of cases. The patient we report on here denied alcohol intake and was negative for all HBV markers. HBV DNA may be detected in anti-HBs positive patients who are HBsAg negative. But the presence of HBV-DNA alone, without any antigen expression, never causes active liver disease. Therefore, it was unlikely that our patient had HBV-associated liver disease.

The other reported cases have been related to unknown causes or to the presence of rare factors, such as pharmaceuticals like Thorotrast, anabolic and probably contraceptive steroids, alpha 1-antitrypsin deficiency, hemochromatosis, tyrosinosis, and nutritional deficiencies.

Hepatocellular carcinoma (HCC) is rare in autoimmune liver disease, specifically chronic active hepatitis of the autoimmune type (10–17) and primary biliary cirrhosis (8, 9).

At least 75% of HCC cases are associated with cirrhosis. The precise relationship between cirrhosis and HCC is not known. Cirrhosis is invariably preceeded by inflammation, cell injury, and cell death; these processes are associated with the formation of oxygen radicals and reactive aldehydes which are mutagenic and consequently may contribute to neoplastic transformation in cirrhosis (18–20). Proliferating cells in chronic liver disease and cirrhosis probably have a higher susceptibility to carcinomatous transformation, as exemplified by increased selection pressure from partial hepatectomy in animal models (21). HCC complicates cirrhosis of the liver in between 5% to 20% of cases (22–23). The incidence of HCC varies according to the etiology of the cirrhosis.

To our knowledge, only 11 cases of HCC associated with autoimmune chronic active hepatitis have been reported in the literature (10–17). Okuda et al did not find any autoimmune chronic liver disease in 113 nonalcoholic patients with hepatocellular carcinoma (24). In a recent review of 124 patients at the Mayo Clinic with autoimmune chronic active hepatitis, 3 had clinically apparent HCC (17).

The patient reported on here developed HCC 21 years after the onset of autoimmune hepatitis.

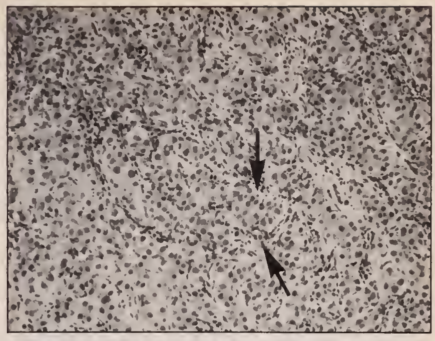

Fig. 1. Liver biopsy specimen showing well-differentiated hepatocellular carcinoma. Portal tracts and terminal hepatic venules are absent. Focally, tumor cells form multicellular thick cords (arrows). Fibrous stroma and inflammatory cells between trabeculae are increased (H & E, original magnification ×40).

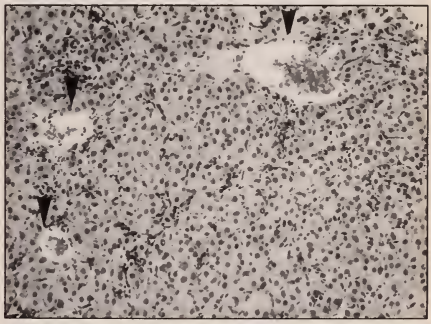

Fig. 2. Increased number of vascular channels (arrowheads) within hepatocellular carcinoma (H & E, original magnification ×40).

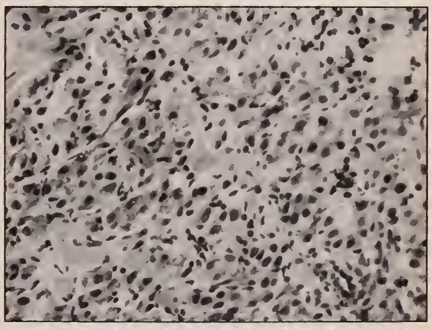

Fig. 3. Hyalinized bands of fibrous stroma extending between neoplastic hepatocytes (H & E, original magnification ×100).

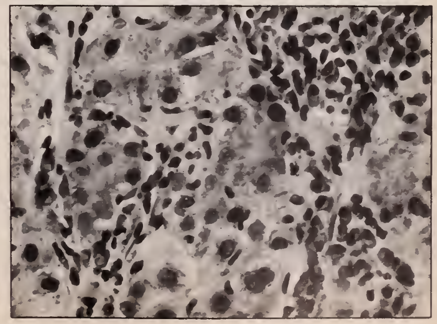

Fig. 4. Inflammatory cells infiltrating tumor are predominantly plasma cells (H & E, original magnification ×250).

Her symptoms were for the most part controlled by prednisone. Long-term use of azathioprine has been associated with the appearance of malignancy (25); our patient was treated with azathioprine for only 2½ years. The tumor of our patient was a well-differentiated carcinoma. Cytologically, the tumor cells revealed minimal pleiomorphism and hyperchromatism, and rare mitotic figures. Plasma cells were abundant and thin fibrous strands were between the neoplastic hepatocytes, arranged in trabeculae. These features have been observed in fibrolamellar HCC (26, 27). However, the tumor cells did not exhibit deeply eosinophilic cytoplasm, characteristic of fibrolamellar HCC. Therefore, the diagnosis of trabecular HCC was made. The most common histologic type of HCC in women over 40 years of age is trabecular carcinoma, representing 54% of cases (27). Of the cases of autoimmune chronic active hepatitis reported, one was a moderately differentiated HCC (11), and one produced bile (12), and was therefore probably also a well-differentiated HCC. The pathologic details of the remaining published cases were not reported.

The prolonged survival and steroid-induced control of disease activity may become important factors in increasing the incidence of HCC in patients with autoimmune chronic active hepatitis. Therefore, as with cirrhosis caused by HBV or alcohol, screening should also be performed for early detection in patients with cirrhosis of the autoimmune type.

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The Formulary

Bernard Mehl, D.P.S., editor

This new feature is intended to provide readers with information on newer therapeutic agents and to review interesting or controversial topics in drug therapy. The topics will be selected from the many issues in drug therapy discussed by the Mount Sinai Pharmacy and Therapeutics Committee. The opinions and actions of the Committee will be presented when appropriate. For each agent the cost for the customary course of treatment will also be included.

Initiating this column are two reviews, one of the drug lisinopril, and another on leuprolide plus flutamide. Both have recently been approved as additions to the Mount Sinai Medical Center Formulary.—Bernard Mehl, D.P.S., Secretary, Pharmacy & Therapeutics Committee

Lisinopril:

A New ACE Inhibitor for the Treatment of Hypertension and Congestive Heart Failure

LAWRENCE CHODOFF, PHARM. D.

LISINOPRIL (Zestril, Stuart; Prinivil, Merck Sharp & Dohme) is an orally active angiotensin-converting enzyme (ACE) inhibitor approved for use in the treatment of hypertension (1). Although not FDA-approved for this indication, this agent, like other members of its class, has also been shown to be of value in the management of congestive heart failure (2, 3). This review focuses on the pharmacology and therapeutics of lisinopril, highlighting the ways in which this agent differs from other ACE inhibitors (captopril and enalapril) currently available in the United States.

Lisinopril is a lysine derivative of enalaprilat, the active metabolite of enalapril. However, unlike this metabolite, lisinopril does not require biotransformation to an active metabolite. Unlike captopril, the molecule does not contain the sulfhydryl moiety, which has been implicated as the cause of a number of unwanted effects associated with captopril therapy, including neutropenia and proteinuria (4, 5). Like other ACE inhibitors, lisinopril produces its antihypertensive activity by inhibiting the formation of angiotensin II, leading to vasorelaxation and reduction of aldosterone-mediated salt and water retention.

After oral administration, lisinopril is slowly and partially absorbed (25%–29%), reaching peak serum levels after approximately 6 hours. Concurrent administration with food does not diminish oral bioavailability, but bioavailability may be reduced in patients with congestive heart failure (6). The drug is not bound to plasma proteins and is excreted primarily unchanged in urine and feces. Unchanged drug is excreted by glomerular filtration (mean renal clearance 106 mL/min), with a mean half-life of 12.6 hours among patients with normal renal function (7). This long half-life relative to captopril (1.7 hours) and enalapril (11 hours) allows for once-daily administration of lisinopril across the entire dosage range of 5–80 mg/day without concern for the end-of-dose failure associated with enalapril. Accumulation of lisinopril in patients with renal impairment is significant (8); prolongation of its half-life to 48.7 hours has been observed among

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patients with creatinine clearance less than or equal to 30 mL/min, with serum levels 2–4 times those observed in patients with normal renal function. Surprisingly, drug accumulation is not associated with hypotension or excessive toxicity (9). However, smaller initial doses (for example, 2.5–5 mg) are recommended in the presence of renal impairment.

Efficacy in Hypertension. Numerous studies have documented the efficacy of lisinopril in both short-term and long-term (up to one year) management of essential hypertension (1). In one double-blind multicenter study of 490 patients with mild to moderate hypertension, lisinopril 20–40 mg/day was shown to be comparable to atenolol 50–200 mg/day in reducing diastolic pressure and significantly superior to atenolol in reducing systolic pressure ($P < 0.01$) (10). Addition of hydrochlorothiazide caused further reduction in both groups, with significantly more patients in the atenolol group (43.4% vs. 32.5%, $P < 0.05$) requiring addition of the diuretic during the 24-week study period. Other trials comparing lisinopril to metoprolol (11) or nifedipine (12) in patients with mild to severe hypertension demonstrate similar excellent results. Among older patients and patients with renal impairment, lisinopril has allowed excellent control of blood pressure for up to one year without evidence of diminution in glomerular filtration rate or cardiac abnormalities (13, 14).

Efficacy in Congestive Heart Failure. Fewer studies have assessed the role of lisinopril in the treatment of congestive heart failure. One multicenter placebo-controlled study among 130 patients with New York Heart Association (NYHA) grade II–IV failure on digoxin or diuretics showed that lisinopril significantly increased treadmill exercise time ($P < 0.01$) and ejection fraction ($P < 0.01$) after 12 weeks of therapy with doses of 5–20 mg/day (15). Patients reported significant improvement in symptoms, including dyspnea and fatigue.

In a double-blind comparison with captopril among 129 patients, both drugs were shown to be effective in prolonging treadmill exercise time. However, lisinopril 5 mg once daily was shown to be superior to captopril 12.5 mg three times daily in prolonging exercise tolerance ($P < 0.05$) and increasing ejection fraction ($P < 0.05$) (16). Both drugs were well tolerated with few adverse effects. However, increases in blood urea nitrogen (18% vs. 5% incidence) and serum potassium (26% vs. 11% incidence) were more common among patients in the lisinopril group owing to more sustained ACE inhibition.

Side Effects. Lisinopril is usually well tolerated; side effects are infrequent and rarely require discontinuation of therapy. In a review of 1165 hypertensives, the most frequently reported adverse effects were headache (6.2%), dizziness (5.6%), cough (3.4%), and diarrhea (3.1%) (17).

Among 311 patients with congestive heart failure, dizziness (9.6%) and diarrhea (6.1%) were most frequently reported. These effects occurred more frequently than with captopril (dizziness 6.2%, diarrhea 1.5%) among patients with congestive heart failure.

Neither proteinuria nor neutropenia have been reported among patients treated with lisinopril. Angioedema has been reported to occur after administration of all ACE inhibitors, including lisinopril (0.1%); patients should be observed closely during initiation of therapy. Although the overall frequency of reports of adverse effects appears greater with lisinopril, the paucity of controlled comparative studies between ACE inhibitors prevents a firm conclusion from being drawn at this time.

Cost. Therapy with lisinopril is at present less costly than with captopril or enalapril.

Average Wholesale Price,
Drug Topics Red Book 1989

Agent	Cost per month
Captopril 25 mg three times daily	$36.00
Enalapril 10 mg twice daily	$40.20
Lisinopril 10 mg once daily	$18.00

Lower cost, plus the expectation of improved patient compliance associated with once-a-day administration, makes lisinopril a valuable new addition to our formulary.

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Leuprolide plus Flutamide:

Combined Androgen Blockade in the Treatment of Advanced Prostate Cancer

LAWRENCE CHODOFF, PHARM. D.

THE DEPENDENCE of adenocarcinomas of the prostate on androgens was first described in 1941 as a result of the pioneering work of Huggins and Hodges (1). Since then orchiectomy and various modes of hormonal manipulation have been the mainstay of palliative treatment of advanced prostate cancer, the administration of estrogens or diethylstilbestrol (DES) being the most frequently employed. Despite good results with these interventions in retarding disease progression, the medical and psychological trauma of orchiectomy, plus the frequent side effects of DES therapy (nausea, edema, gynecomastia, thromboembolism), prompted the search for alternative therapies.

The concept of combined androgen blockade (often erroneously referred to as "total" or "complete" androgen blockade) refers to inhibition of all androgen activity by blocking the synthesis and release of adrenal and testicular androgens and inhibiting intracellular biochemical steps that mediate androgen action on target tissues (2). The administration of the gonadotropin-releasing-hormone (GnRH) agonist leuprolide (Lupron, TAP Pharmaceuticals), in combination with flutamide (Eulexin, Schering), a "pure" antiandrogen, has been shown to produce an excellent clinical response in patients with advanced stage D_2 cancer of the prostate, with minimal adverse effects and improved quality of life (3, 4).

The Contribution of Leuprolide. Leuprolide is a synthetic analogue of GnRH. Following parenteral administration, leuprolide causes an initial increase in secretion of leuteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in transient elevation of levels of circulating testosterone and dihydrotestosterone. This is followed after 2–4 weeks by a marked decrease in the serum levels of these hormones to castrate levels. GnRH agonists such as leuprolide cause this paradoxic effect by producing a down-regulation of the receptors in the pituitary and testes (5). This down-regulation results in decreased production of LH by the pituitary and of testosterone by the testes.

The value of leuprolide as monotherapy for advanced prostate cancer was demonstrated in a multicenter randomized comparison with DES among 199 patients (6). This study indicated that the two drugs have similar efficacy in treating prostate cancer (86% vs. 85% complete or partial response), but that the group receiving leuprolide experienced significantly fewer serious unwanted gastrointestinal and cardiovascular effects. The one adverse effect that occurred more frequently among patients receiving leuprolide was hot flashes (52% vs. 11%, $P < 0.00001$).

The Contribution of Flutamide. Despite the dramatic reduction in serum levels of testosterone and dihydrotestosterone that occurs after castration or treatment with a GnRH agonist, residual androgens released by the adrenals are left unopposed and are sufficient by themselves to exert an important stimulatory effect on prostate cancer growth (3). Flutamide is a nonsteroidal antiandrogen that lacks any estrogenic or progestational activity. After oral administration, flutamide (or its metabolite) inhibits the uptake of testosterone, or the binding of testosterone or dihydrotestosterone, or both, to the nuclear receptors of target cells. Thus it prevents androgens from exerting their biological effects (7).

Among 72 patients with previously untreated advanced prostate carcinoma, 63 (87.5%) had a favorable response that included reduction or elimination of bone pain and shrinkage of prostatic nodules and resolution of consequent urinary obstruction (8). Gynecomastia developed in 53 of these patients, and was the only serious side effect encountered. In another trial that compared flutamide to DES, 1 mg daily, among 15 previously untreated patients, neither agent displayed significant superiority (9).

Clinical Confirmation of Combined Blockade. Several studies have provided clinical confirmation of the validity of the combined androgen blockade approach (3, 10). One large multicenter study among 603 previously untreated patients with Stage D_2 disease compared leuprolide plus placebo, versus leuprolide 1 mg daily as a subcutaneous injection plus flutamide 250 mg orally three times daily (4). Patients receiving combination therapy had a longer progression-free survival (16.5 vs. 13.9 months, $P = 0.039$) and an increase in the median length of survival (35.6 vs. 28.3 months, $P = 0.035$) over those who received leuprolide alone during 42 months of observation. Both treatments were well tolerated. Hot flashes occurred among more than 60% of patients in each group; only diarrhea was more frequent among the group receiving flutamide (13.6% vs. 4.9%).

Thus, combined androgen blockade provides successful palliative therapy for patients with advanced prostatic cancer, while sparing them the trauma of surgical orchiectomy and the frequent disabling or life-threatening side effects of DES administration. Parenteral therapy has been made easier by the recent introduction of a long-acting depot formulation of leuprolide (Lupron Depot, TAP Pharmaceuticals) suitable for intramuscular administration once monthly.

Cost. Despite the appeal of combined androgen blockade, one's enthusiasm must be tempered by the realization that therapy with leuprolide and flutamide will cost the patient at least $500 per month, compared with $5 per month for DES therapy.

Average Wholesale Price,
Drug Topics Red Book 1989

Agent	Cost per month
DES 3 mg once daily	$4.14
Lupron 1 mg subcutaneously once daily	$321.30
Lupron Depot 7.5 mg intramuscularly once monthly	$321.30
Flutamide 250 mg three times daily	$167.08

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Bilateral Calcaneal Intraosseous Lipomas:

A Case Report

Edward M. Rosenblatt, M.D., Joel Mollin, M.D., and Ibrahim Fikry Abdelwahab, M.D.

Osseous lipomas are the rarest primary tumors of bone, with an incidence of less than one lipoma per 1000 bone tumors (1). Despite the abundance of fat in the medulla of the bone, there is apparent paradoxical rarity of the occurrence of lipomas in bone. This report presents a case of bilateral calcaneal intraosseous lipomas, which are extremely rare; to the best of our knowledge this is the first report of such lipomas.

Case Report

A 40-year-old black man came to the emergency room for vague pain in his left foot. He had sustained trauma to this foot a few months earlier. Clinical examination of the left foot revealed tenderness on the base of the fifth metatarsal bone. Plain radiographs ruled out any fractures. However, an oval lucent lesion with sclerotic margin and central calcifications was noted in the anterior part of the calcaneus (Fig. 1). Computed tomography was then performed and confirmed the findings of the plain radiograph. Incidentally noted was an identical lesion in the right calcaneus (Fig. 2). No surgical treatment was pursued and the patient was scheduled to be followed up in the Orthopedic Outpatient Clinic.

Discussion

Skeletal lipomas are classified into three groups based on location within the bone. In decreasing frequency, these groups are the paraosteal, the intraosseous (intramedullary), and the intracortical (2). Calcaneal lipomas belong to the intraosseous variety and constitute 15% of these lesions. The most common sites of intraosseous lipomas are the proximal segment of the fibula, femur, and tibia, where the incidence is approximately 50% (3).

The radiographic appearances of calcaneal lipomas are virtually diagnostic. They usually occur at the junction between the anterior and middle third of the bone between the major trabecular groups and appear as a well-defined lytic area with a sclerotic rim exactly resembling simple bone cysts of the calcaneus in site and radiographic appearances (4). The diagnosis is clinched in one-half to two-thirds of the cases by the presence of a central calcified focus, which on histologic examination is an amorphous collection of calcium without any osteoblastic activity (2).

Bilaterality. The case presented herein fits this classic description. However, the main purpose for presenting this report is the bilaterality of the lesion. Searching the literature, we could not locate a similar case. All reported bone lipomas, except for a single case report of a patient with hyperlipoproteinemia, have been solitary. Even in this reported case, the bilateral lipomas were in both tali and tibiae, and not in the calcaneus (5).

Pitfalls in Computed Tomographic Diagnosis. The utilization of computed tomography in the evaluation of musculoskeletal lesions has allowed for the definite diagnosis of intraosseous lipomas, obviating the need for biopsy confirmation for such benign-appearing tumors. The

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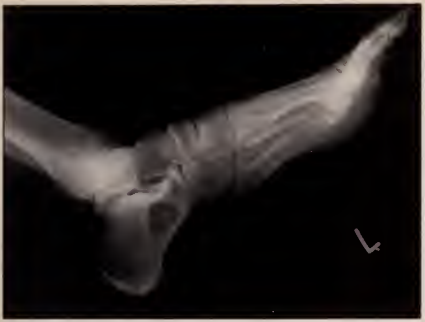

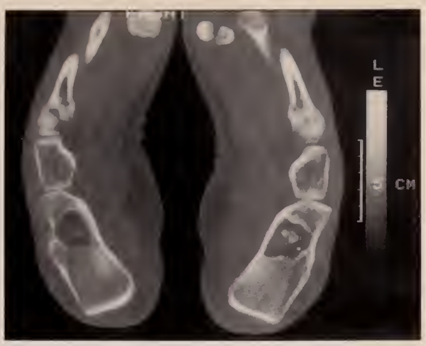

Fig. 1. **Left** Lateral view of left foot showing oval lucency in anterior part of calcaneus. Lesion is sharply defined, with sclerotic margin and central focus of calcification. Fig. 2. **Right** Computerized tomography of both calcanei demonstrating identical lesions in anterior part of bones. Each lesion involves whole diameter of bone and has sclerotic margin and central focus of calcification.

identification of the fairly uniform fatty composition of the lesion based on appropriately negative CT numbers virtually confirms the diagnosis (6). However, pitfalls in the approach have been recognized, and include the observation that the atrophic residual bony trabeculae that commonly course through the lesion can result in artifactually high CT numbers if averaged into the measurements (7). Conversely, areas of fatty degeneration or collections of fat-laden histiocytes that occur in lesions other than lipomas can give low CT numbers (3). The degree of certainty is definitely increased with the CT identification of a central calcified focus within the intraosseous lipoma of the calcaneus. In the case reported, the measurements which were taken throughout of the right and left calcaneal lesions confirmed their fatty consistency. Additionally, the calcified central foci in both lesions were clearly identified.

Histopathologically and biochemically, intraosseous lipomas are indistinguishable from the vastly more common soft-tissue lipomas. There have been no reports of malignant degeneration or metastases of osseous lipomas (8). Hence, conservative therapy, usually simple observation, is the accepted mode of treatment.

Differential Diagnosis. Intraosseous lipomas of the calcaneus have to be differentiated from other benign lesions: simple bone cyst, pseudocyst of the calcaneus, aneurysmal bone cyst, encystified infarct, chondroblastoma, chondromyxoid fibroma, and, less commonly, eosinophilic granuloma and fibrous dysplasia.

Most of these diagnostic considerations usually occur in the first and second decades, though simple bone cysts and encystified infarcts can occur in adults and can be confused with the intraosseous lipoma. Simple bone cysts usually abut the lateral wall of the bone and extend one-half to two-thirds of the width of the bone. On the lateral roentgenogram it is centered at the base of the calcaneal neck just inferior to the anterior portion of the posterior facet.

Most simple bone cysts have a characteristic shape. The anterior margin of the cyst is usually straight and vertical. The posterior border is typically curvilinear, paralleling the bone trabeculae in the posterior part of the bone. The central portion of the simple bone cyst is almost completely devoid of bone or central calcifications. Encystified infarcts were ruled out because their attenuation is higher than lipomas in CT.

Summary

A case of bilateral intraosseous calcaneal lipomas in a 40-year-old man is presented. Because of the benignancy and the virtually diagnostic appearance of this lesion radiographically, a bone biopsy was not performed. This may be the first case of bilateral involvement of the calcaneus by intraosseous lipomas.

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Student Corner

Dilatation of the Biliary Ductal System: Choledochal Cysts

Sridhar Mani, B.S.

Idiopathic dilatations of the biliary ductal system are a heterogeneous group of disorders among which choledochal cysts play an important role. Their early diagnosis and management prevents later development of irreversible complications. Importantly, these cysts are increasingly being recognized in the Western hemisphere, and accurate pre- or perinatal diagnosis is extremely valuable in preventing future cholestasis and malignancy. These cysts must be differentiated from other types of heretofamilial liver cysts such as the fibropolycystic disease complex and Caroli's disease, although choledochal cysts may coexist with the latter. Recent experience with the management of a patient with a choledochal cyst prompted this report and a review of the pertinent literature.

Case Report

A 30-year-old married woman was admitted to Beth Israel Medical Center on November 17, 1988 with a three-week history of intermittent crampy epigastric and right upper quadrant pain. There was no history of fever, chills, nausea, vomiting, jaundice, or weight loss.

Careful questioning revealed that at age 4 years, she experienced similar episodes of crampy abdominal pain and was told that she had a "gallbladder problem or twisted intestines." At age 26 years she experienced transient episodes of mild right upper quadrant pain.

On physical examination there was a tender epigastric mass. Liver and spleen were not palpable. Bowel sounds were normal. The rest of the examination was normal. ERCP (Fig. 1) revealed a markedly dilated common bile duct consistent with a choledochal cyst.

At operation, the dilated common bile duct measured 3 cm and the gallbladder did not contain calculi. A cholecystectomy and choledochocystojejunostomy Roux-en-Y was performed. Her postoperative course was uneventful.

Choledochal Cysts

Choledochal cysts, a subset of cystic dilatation of the biliary ductal system, are aneurysmal or cystic dilatations of the common bile duct or choledochus. They were initially described by Vater and Ezler in 1723 (1); however, the first accurate description of the condition is credited to Douglas in 1852, who described a 17-year-old girl with complaints of "pain in the liver, icterus in a moderate degree, and a swelling gradually increasing in size in the right hypochondria region" which were accompanied by fever, wasting, and edema of the legs. The patient died two weeks later and autopsy revealed "half a gallon of ill-smelling gall in an excessively enlarged choledochus" (2, 3).

The first successful treatment was by Swain, who carried out a cholecystojejunostomy using a Murphy button in 1895 (3, 4). In 1897, Brun and Hartman managed a 3-year-old girl on external drainage followed 4 months later by a choledochoenterostomy (3, 5). The first successful excision of a choledochal cyst was performed by McWhorter in 1924, and in the same year Neuge-

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Presented at Surgical Grand Rounds, Beth Israel Hospital, April 7, 1989. Written when the author was a third-year medical student at The Mount Sinai School of Medicine. Address reprint requests to the author at 30 Waterside Plaza, Apt. 23A, New York, NY 10010.

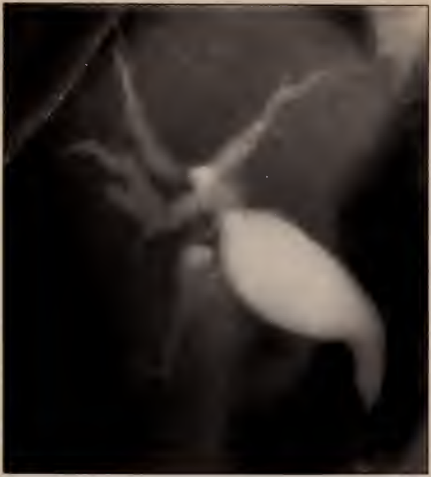


Fig. 1. ERCP revealing type I choledochal cyst.

bauer advanced the first correct preoperative diagnosis (3, 6, 7).

In a landmark paper suggesting a classification system for different types of choledochal cysts, Alonso-Lej et al reviewed another 161 new cases, bringing the total number to 403 by 1959 (8). Flanigan reviewed 955 cases, which included 455 new cases observed in the period spanning 1969 to February 1975 (9). The Japanese literature revealed similar reports, and now two-thirds of the reported cases originate from Japan (10–12). In 1980, Yamaguchi (13) analyzed a total of 1,433 cases—1,204 cases reported in the Japanese literature between 1966 and 1978, 224 cases reported by Koboyashi (10), and 5 new cases. As of 1985, the number of cases exceed 1,500 (14).

Epidemiology. Choledochal cysts occur most commonly in Japan. Worldwide estimates of incidence range from 1:13,000 to 1:2,000,000 (15–17). One Japanese review cites an incidence of about 1:1000 (18). These cysts are primarily a disease of infancy and childhood (15, 19, 20); around 25%–50% of all cases are diagnosed in infants less than 1 year of age, 40%–60% of all cases in children less than 10 years of age, and 8%–17% in patients older than 40 years of age. The female-to-male ratio in most major series is approximately 3–4:1 (9, 13); however, one Japanese series reported no sex predominance (15).

The familial nature of choledochal cysts is uncertain. One Japanese study suggested that there may be a hereditary component to congenital biliary ductal dilatation, due to an abnormal junction of the pancreaticobiliary ductal system or congenital biliary ductal dilation that is either X-linked dominant or an autosomal dominant trait with relatively low penetrance (21).

Etiology: Congenital Theories. Congenital theories of cyst development broadly focus on weakness of the wall of the common bile duct or obstruction to bile outflow, either from the common bile duct proper, or the choledochoduodenal junction, or both. Local anatomic malformation in a specific segment of the duct, rather than obstruction per se, has also been postulated as a basis for the development of choledochal cysts. Most authors consider obstruction to be the result rather than the cause of cyst formation (3, 22). Obstruction to bile outflow as a sole cause of cyst formation has not received popular support; however, among all proposed mechanisms, elegant congenital neurodysplastic theories are receiving greater attention. Autonomic neurodysplasia, a condition similar in nature to a congenital aganglionosis of the colon, may be responsible for common bile duct obstruction (3, 23, 24).

In two recent papers, Kusunoki and colleagues (25, 26) have corroborated laboratory evidence suggesting postganglionic neural dysfunction and oligoganglionosis in the narrow portion of the choledochus. Single specimen studies that compared the choledochal cyst with the normal common bile duct utilizing CCK–octapeptide and acetylcholine produced smaller contractions in the strips obtained from the narrow portion of the cyst than in those strips from the dilated portion and normal common bile duct, thus suggesting a lack of postganglionic cholinergic neurons. Nicotine did not induce contractions in the narrow portion of the cyst, indicating an absence of nicotinic receptors, which are mainly located on postganglionic cholinergic cell bodies.

In strips obtained from normal common bile duct and dilated portion of the cyst, gamma-aminobutyric acid (GABA) induced atropine-sensitive, tetrodotoxin-sensitive, concentration-dependent contractions through bicuculline-sensitive, furosemide-sensitive GABA receptors located on postganglionic cholinergic neurons. GABA did not induce any contraction in strips obtained from the narrow portion of the cyst. This further supports the view that postganglionic cholinergic cell bodies are not present, or are at least decreased, in the narrow portion of the cyst. On histologic examination, the number of ganglion cells were markedly decreased in the same portion (25).

Subsequently, Kusunoki et al. (26) investigated five cases of Todani type I choledochal cysts (see "Classification," below). They found ganglion-cell ratios of narrow-to-dilated portion of 0.271, and a decrease in total number of ganglion cells in the narrow portion significantly different from the dilated portion ($P < 0.05$), regardless of the nature of the pancreaticobiliary junction. These findings, although not universally confirmed, strongly support the concept of oligoganglionosis in the distal choledochus.

Junctional anomalies include the common channel syndrome (27–34), secondary inflammatory changes in adjacent surrounding tissue (3), atresia without recannulation (3, 35), and unidirectional valve mechanism at the ampulla of Vater (3, 7).

The common channel syndrome assumes a long common duct which escapes the antiregurgitant mechanisms of the duodenal wall (27–34). Postmortem and radiological studies indicate that common channels of varying lengths are normal findings in 58%–90% of cases (19, 36–39). Hence, it is possible to have a long common duct with preservation of antireflux mechanisms. An abnormal junction of the pancreaticobiliary ductal system is only thought to be significant when the criteria of an abnormally long common duct, reflux, and possibly angulation at the junction of the bile and pancreatic ducts are present. These criteria have not been strictly defined and vary from series to series (27). Common duct lengths of greater than 1 cm in adults with symptoms suggestive of mild intermittent reflux have generally been used as positive criteria for common channel syndrome (27, 28). In children, a length greater than 4 mm has been implicated as a significant elongation of the common channel (29). Experimentally induced elongation of common channel in puppies seems to support the concept of common channel syndrome (3). Authors suggest early surgery if abnormal junction of the pancreaticobiliary ductal system is demonstrated by ERCP in order to prevent reflux and neoplastic complications resulting from this anomaly (27, 33, 39, 40).

Yotsuyanagi (41) attempted to combine all congenital theories into one unified hypothesis. He postulated that during the normal asymmetric epithelial recanalization after duct occlusion in the embryonic period, abnormal arrests of varying degrees between proximal and distal recanalization could occur, leading to a variety of closely related conditions ranging from complete atresia to mildly dilated proximal ducts. He postulated that choledochal cysts occupied one segment of this spectrum of recanalization abnormalities or arrests.

Several authors have postulated distal obstruction with proximal duct wall weakness as etiologic factors for the development of cysts (3, 8, 42). Acquired cysts in adulthood have been reviewed by Spitz (3); however, such cases are rare, although their etiogenesis is mostly of a mechanical nature. Certain Todani type III cysts (see "Classification," below) are interesting in that they may actually reflect a form of congenital duodenal duplication. This is an attractive hypothesis that needs further study (43).

Classification. Essentially two classification systems exist: the Alonso-Lej (8), dating from 1959 (Fig. 2), and the Todani (44), published in 1977 (Fig. 3). Broadly speaking, the latter scheme expands on the former by including intrahepatic biliary cysts, and is the most often used.

In the Alonso-Lej scheme, type A is the most common and type C the least common (8). In the Todani scheme type I makes up 80%–90% of cases; type II, up to 2% of cases (corresponds to Alonso-Lej type B); type III, 1.3%–6% of cases (corresponds to Alonso-Lej type C); type IV, 19% of cases. Type IV B is the least common (8, 9, 13, 14, 44).

In 1958 Caroli described cystic involvement of intrahepatic ducts only (45). In line with the Alonso-Lej scheme (1959), Caroli's disease came to be known as type IV choledochal cysts. However, current formulations place Caroli's disease as type V choledochal cysts (single or multiple) within the Todani scheme (14, 19, 44, 45). Oldham estimates that ⅔ of patients with type V cysts have concurrent type IV A cysts (46, 14).

Histology and Histopathology. Cyst wall thickness varies from approximately 1 mm to greater than 1 cm. Histologically, the cyst wall is composed of incomplete epithelial lining with scattered cuboidal or columnar cells. Type III choledochal cysts are an exception to this finding in that they are lined by either duodenal mucosa or bile duct mucosa. Deeper layers tend to be fibrotic with abnormal dispersal of elastic tissue and smooth muscle (14). Liver biopsy tends to be abnormal in 60% of patients, usually revealing evidence of biliary cirrhosis, atresia, or portal fibrosis (47).

Suruga (48) has described three stages in the histogenesis of choledochal cysts. Stage I is characterized by edema and poor musculature surrounding the duct. Stage II is characterized by inflammatory and granulomatous infiltrates. Stage III consists of a fibrotic, thickened duct wall with

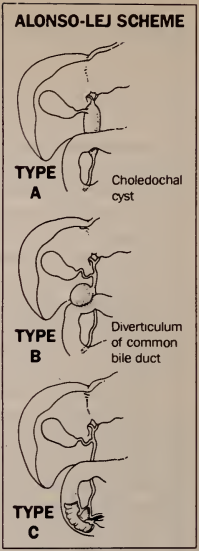


Fig. 2. Left Alonso-Lej classification of 3 types of choledochal cysts. Type A is the most common, type C, congenital form, the least common. Adapted from Alonso-Lej F, Rever WB Jr, Pessagno DJ (ref. 8). **Fig. 3. Right** Todani classification, now the most often used. Type I constitutes 80%–90% of cases, type II, up to 2% of cases (corresponds to Alonso-Lej type B); type III, 1.3%–6% of cases (corresponds to Alonso-Lej type C); type IV, 19% of cases. Type IVB is the least common. Adapted from Todani T, Okajima K, Tabichi K (ref. 44).

or without adhesions. At this point there may be hypertrophy of surrounding musculature. With time, dysplastic changes may be come evident. In keeping with these mucosal changes, intestinal metaplasia may also be evident.

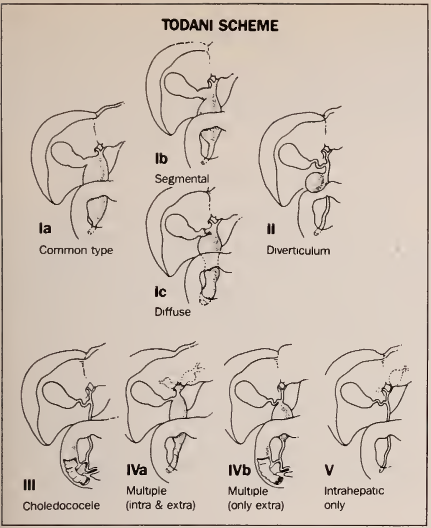
Clinical Presentation. The classic triad of pain, abdominal mass, and jaundice occur in about a third of patients, with a range of 13%–68% (8, 13, 14). Typically this triad of symptoms is present in older children who have a history of intermittent fever, jaundice, and abdominal pain. In the Yamaguchi series (13), 50% of patients initially had abdominal pain, 45% had jaundice, and 36% had an abdominal mass. However, in the Lee et al series (49), 64% initially had jaundice, 58% had an abdominal mass, and 55% had abdominal pain (49). In both series, more than 60% of patients had more than one symptom. Duration of symptoms ranged from less than 4 weeks (20%) to more than 4 years (20%); less than 4% of patients have ongoing symptoms lasting more than 40 years (14).

One must consider choledochal cysts in infants who are chronically icteric with high unexplained direct bilirubin levels. Rarely, bile peritonitis may be the initial presentation in neonates. Importantly, older children do initially have obstructive jaundice and vomiting. The latter is usually due to either infection or duodenal obstruction (3). Recurrent pancreatitis and ascending cholangitis are uncommon initial symptoms in children and adults (14, 50–53). Hyperamylasemia has been noted in less than 30% of patients with cysts. These elevations tend to be mild, although high levels of amylase have been documented in cyst fluid. In such cases, authors have advised cyst excision in order to avoid the development of cholangitis and hyperamylasemia (54, 55). Clinically, cholangitis, biliary cirrhosis, and pancreatitis are important in association with cysts.

Diagnosis. Precise radiologic techniques are available that delineate the cystic cavity with over 90% accuracy. Correct preoperative diagnosis ranges from 27% to 80% depending on the series (9, 14).

Ultrasonography is a safe, simple, noninvasive technique that provides information regarding cyst size, location, contour, and composition (stones). Demonstration of a nonpulsatile cystic mass riding deep into the porta hepatis with branching pattern is virtually diagnostic of a type I cyst.

In one study, 12 of 15 patients with choledochal cysts were accurately diagnosed using high-quality real-time sonography, but in the other 3 patients, the technique was misleading (55). The CT scan has similar accuracy but in many cases is clearer in delineating biliary origin. In fact, one study proposes that contrast



layering within the cyst cavity gives a definitive diagnosis when clinical or other imaging features may not clearly establish the diagnosis (56). Many authors have suggested using sonography initially and definitive intervention only when sonography has failed to accurately describe the lesion (55, 57–60).

Definitive diagnosis may be achieved using either endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) (14, 61). The former technique has a reported accuracy rate of over 90% (14, 46). However, ERCP is technically more difficult to perform and may precipitate traumatic pancreatitis, especially in the young. During surgical exploration, definitive diagnoses of unsuspected cysts (type II or III) can be achieved via intraoperative cholangiography (3, 14).

Complications. Long-standing obstruction leading to ascending cholangitis and biliary cirrhosis has been recognized in association with biliary cysts. Cholangitis seems to be stasis induced, often occurring with liver abscesses and not always relieved by surgery.

Primary cyst stones have been reported and are estimated to occur in 8% of patients with long-standing choledochal cysts. The stones are usually multiple and may occur either in the intrahepatic or extrahepatic biliary ductal system (3). Pancreatitis is a common complication of long-standing cysts and is thought to be secondary to reflux (9, 62). Portal hypertension is uncommon with small cysts; however, larger cysts compress the porta hepatis, leading to hypertension, aneurysms, portal stasis, and thrombosis, and in some cases to severe gastrointestinal hemorrhage (62).

Spontaneous cyst rupture is extremely uncommon and is usually secondary to trauma (9, 63). Cysts have been reported to rupture during pregnancy and in one patient rupture during labor has been documented (9).

Other less well reported complications and associated findings with biliary cysts include acquired dysfibrinogenemia (64), hematobilia secondary to a pseudoaneurysm complicating a choledochal cyst (65), congenital hepatic fibrosis and renal polykystosis (66–68).

Biliary carcinoma in association with cysts is a recent well-documented occurrence. Historically, by 1975 Flanigan had documented 24 cases in association with biliary cysts (9). By 1977, 33 cases of biliary carcinoma had been reported, with 3 additional cases of intrahepatic biliary ductal carcinoma and 5 cases of hepatic and pancreatic carcinoma. By 1985, Voyles reviewed a total of 67 cases reported in the world's literature (69). By 1988, authors had documented another 60 cases of biliary carcinoma, of which 16 cases were gallbladder cancers; 2 cases of common bile duct cancer and one case of pancreatic cancer associated with the hepatobiliary fibropolycystic disease complex; 4 cases of gallbladder cancer associated with abnormal junction of the pancreaticobiliary duct but without choledochal cysts (70–78).

The incidence of biliary carcinoma is 0.0007% to 0.041% of all hospital admissions (79). The incidence of biliary carcinoma in persons with biliary cysts is 2.5%, which is significant ($P < 0.001$) in comparison to the occurrence of biliary carcinoma in the general population (9). The male-to-female ratio is approximately 1:2, with a mean age of 32 years and a range of 17 to 70 years (9). In the Voyles series (69), 52% of all cysts were diagnosed during the first decade of life; however, only 0.7% of these patients subsequently had carcinoma, compared with 6.8% in the second decade and 14.3% after the age of 20 years. All the cases of carcinoma documented in cysts detected in the first decade of life were diagnosed more than two years after the internal drainage procedure; however, no such temporal relationship between initial operation and diagnosis of carcinoma was observed in the second decade of life and beyond.

These age-related risks suggest age-adjusted strategies for the management of biliary cysts. Therefore, Voyles suggests that excision and hepaticojejunostomy should be the procedure of choice whenever feasible (69).

Most associated carcinomas of the biliary system are adenocarcinomas. Squamous cell carcinoma occurs less frequently. Eighty-four percent of all carcinomas occur with cysts of type I or type IV B (80). Fifty-seven percent of all carcinomas occur within the cyst wall, and the most common location is the posterior wall of the cyst. Most (57%) of these patients with carcinoma had at some time undergone an internal drainage procedure. The most common procedure in such patients was choledochocystoduodenostomy (80). On average, 50% of reported patients with carcinoma sought treatment an average of 4 years after internal drainage (81).

Risk factors possibly contributing to the development of carcinoma are not fully understood; however, bile stasis and bile-epithelium contact time, superinfection, and age-related intestinal metaplasia in the gallbladder may play important roles in the etiology of cancer (73, 75, 82). The latter theory, postulated as a spectrum of possible changes leading to biliary carcinoma, seems to be the key issue in successful management. The five-year reoperation rates secondary to anastomotic strictures resulting from initial cystenterostomy is 40%–64%, as compared with 1% in patients who have undergone primary excision with proximal bile duct anastomoses (44).

In all cases, cyst excision is advocated, in view of the risk for development of carcinoma, ascending cholangitis, and higher reoperation rates with internal drainage procedures. However, even with all this data, 2 cases of intrahepatic carcinoma after cyst excision have been described so far (83). Yoshikawa claims that malignant changes have occurred in the biliary system on long-term follow-up even after cyst excision (72). In contrast with such observations, Todani et al propose that an increased risk of cancer does not persist except in type IV A cyst, in which carcinoma may occur in other parts of the remaining duct (80).

Management. The treatment of choledochal cysts is surgical and not medical. The key issues in intervention are obstruction and abnormal mucosa. Historically, the initial attempts to treat cysts were directed at only obstructive symptoms until excision was introduced in 1924 by McWhorter (6).

Today most intervention is either via internal drainage procedure or cyst excision. The advantages of cyst excision have been outlined before; however, the disadvantages include prolonged operation time, risk of injury to hepatic artery, portal vein, or pancreatic duct (14, 84). Internal drainage should be reserved for those patients in whom cyst excision is not feasible.

Summary

The case described in this report is typical of a patient with a choledochal cyst. Although common in Japan, such cases are being increasingly reported in other countries. Because diagnosis depends most importantly on clinical suspicion, detailed history taking and appropriate early intervention are mandated. Additional radiologic studies may help confirm the diagnosis. The crucial step in management is deciding between cyst excision and internal drainage. The ultimate decision depends on the individual patient profile. Long-term follow-up is mandated by the increased risk of biliary carcinoma.

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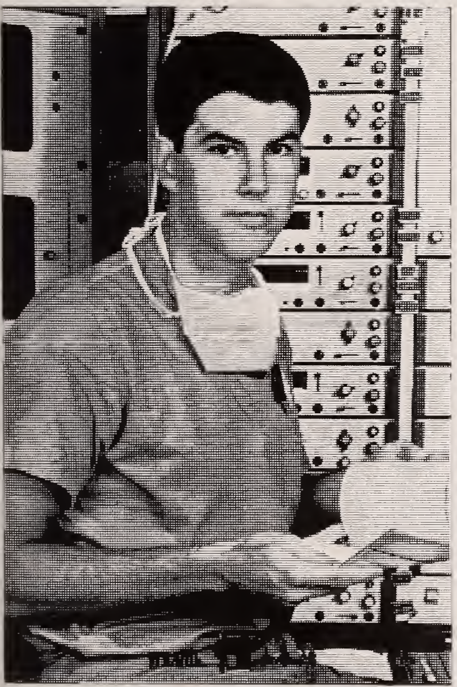

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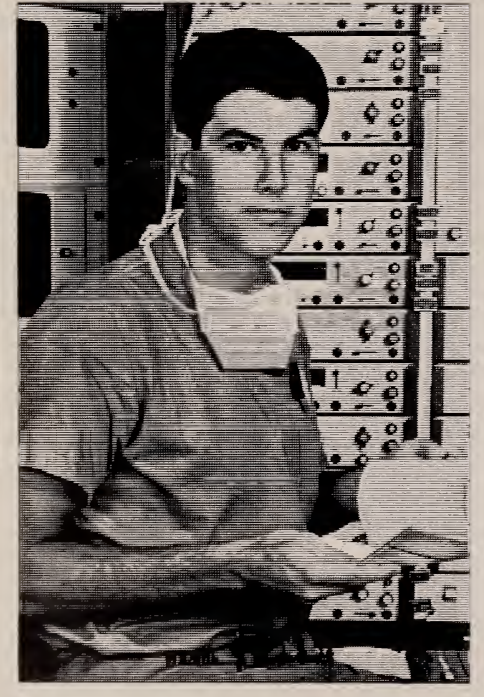

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Introduction

EDWARD J. BOTTONE, PHD
SECTION EDITOR

Sexually Transmitted Diseases

THE MULTIPLE social and clinical dimensions of the premier sexually transmitted disease (STD), the acquired immunodeficiency syndrome (AIDS), are dramatically reflected in the collateral explosion in the "classic" sexually transmitted diseases syphilis, gonorrhea, chancroid, chlamydial and herpes infections. Although one study has suggested a diminution in chlamydial infection among students at a midwestern university (1), stark concern has been unanimously expressed over the increasing incidence of STD across the United States and even globally. Additionally, an apparent association exists between disruption of genital epithelium as a consequence of an STD, and the facilitation of human immunodeficiency virus transmission (2). The global impact of STDs is further reflected in the broadening clinical spectrum of infectious complications of sexual origin and in the enormous burden placed on financial and human resources allocated to prevention and control programs.

There are several populations of high-risk individuals who from time to time intersect and hence not only increase transmission, but are themselves exposed to other infected individuals. These groups comprise young adults (15–24 years old) in Western countries who because of changing social values and behavior are more sexually active, and at greatest risk for exposure to an STD. Infection in many of these individuals is asymptomatic and hence transmissible to other susceptibles. Unfortunately, this population of susceptibles is mainly concentrated in urban areas, where access to each other and to other high-risk groups such as "crack" prostitutes and those with different sexual preferences and practices is amplified. Taken together, these factors have conspired to bring about the alarming increase in STDs; in the United States, the yearly increase has been estimated at 1–2 million new cases of gonorrhea, 4 million new cases of *Chlamydia* with 500,000 to 1 million new cases of pelvic inflammatory disease, 750,000 new cases of genital warts caused by the human papilloma virus (HPV), and 500,000 new genital herpes simplex virus infections (3). Syphilis is estimated to be rising at 100,000 new cases annually, including a profound increase in congenital syphilis, and has sharply risen among black men and women (4).

Concomitant with the escalation in STDs in this era of AIDS and widespread use of illegal drugs is (a) the altered and more progressive course of STDs such as syphilis and herpes in HIV-infected persons, (b) the constancy of the simultaneous occurrence in one person of more than one STD (for instance, syphilis and chancroid, chancroid and gonorrhea), and (c) the emergence of erosive genital lesions due to fusiforms and nontreponema (*Borellia*) spirochetes (Jeff Gilbert, M.D., Senior Medical Specialist, Sexually Transmitted Disease Bureau, New York City Department of Health, personal communication).

In the ensuing papers, written by a stellar faculty of STD experts including William M. McCormack, Max A. Chernesky, Edward W. Hook III, and Col. Edmund C. Tramont, we are apprised of the magnitude of STD-related problems and of changes in the natural history and in some instances the clinical course of these diseases; changes in clinical course may be so great as to obfuscate diagnosis. The reemergence of the forgotten or overlooked venereal disease, congenital syphilis, is also noted. Although chancroid is not dealt with in this issue as a separate entity, its increased incidence in the New York City area (5) and globally (6), where it outnumbers cases of syphilis, is frightening and further testifies to the challenges in control and prevention of sexually transmitted diseases.

This thematic issue on sexually transmitted diseases invites the readership of physicians in all medical disciplines, for these infectious agents are unbridled in their assault on the human body. Diverse in their basic biology, the inciting

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Dr. Bottone is Director of the Clinical Microbiology Laboratories, The Mount Sinai Hospital. The four papers in this section were developed from each author's presentation at the seminar "Sexually Transmitted Diseases" held at the Mount Sinai Medical Center, New York City, on March 23, 1990.

agents of STDs have posed significant diagnostic and therapeutic dilemmas and, further, because of the varied clinical syndromes, have spawned an evolving branch of medicine, venereology.

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Overview:

Sexually Transmitted Diseases

William M. McCormack, M.D.

THE CONTROL of sexually transmitted disease (STD) involves educating persons who are at risk as to modes of transmission and means of primary prevention, including abstinence, selectivity in the choice of sexual partners, and the use of barrier methods of contraception, such as condoms; the detection of infection through either screening of nonsymptomatics or by culture and diagnosis of patients who have symptoms; the provision of effective diagnosis and treatment; and finally, the management of sexual partners: evaluation, education, and treatment.

Screening is a major approach to STD control. The question of who should be screened is a large one. High-risk persons obviously need to be screened, but who is at high risk? Young, sexually active people, and persons who have multiple sexual partners should be so considered. The classic definition of promiscuity, "someone who has more sexual partners than you do," does not hold here. I think that anyone who has more than one recent sexual partner is a candidate for screening.

We should also screen persons who have a history of STDs and women who do not use contraception, which is evidence of risk-taking behavior (cigarette smoking, lack of use of seat belts, or other indexes of risk-taking behavior could also be used). We should also screen individuals who clearly exhibit high-risk behavior, such as prostitutes, their clients, persons who use illegal drugs, and prisoners. Pregnant women are a special population available for screening either in association with termination of pregnancy or as part of prenatal care.

Once it is decided that someone needs to be screened, the microbial agents and infections that should be looked for include human immunodeficiency virus (HIV), syphilis, gonorrhea, and chlamydia; pregnant women should also be screened for hepatitis B.

A major current concern is the relationship of STDs to the acquisition of HIV and the interaction between HIV and STDs. The diagnosis of a sexually transmitted infection indicates high-risk behavior and identifies a person who is at risk for and should be tested for HIV. Surveys among attendees of sexually transmitted diseases clinics have shown a substantial HIV infection rate. In our STD clinic at Kings County Hospital Center in Brooklyn, about 10% of patients are HIV positive.

There is concern that the sexually transmitted diseases that damage dermal or mucosal barriers may facilitate HIV transmission. Data from Africa and from Seattle indicate that genital ulcers are associated with HIV infection (1, 2). It is not clear whether diseases like gonorrhea or chlamydia infection, which can impair the integrity of the cervical mucosa, might also provide increased access for HIV.

In the HIV-infected patient, STDs are an indicator of the kind of sexual activity the patient should preferentially not be engaging in. There is also a concern that HIV may alter the natural history of disease and may affect response to treatment. Whatever influence HIV has on the course of the disease or its response to treatment is due to the immunosuppression produced by HIV, not to HIV infection itself. Thus, the CD4

Adapted from the author's presentation at the seminar "Sexually Transmitted Diseases" held at the Mount Sinai Medical Center on March 23, 1990. From the Departments of Medicine and of Obstetrics and Gynecology, State University of New York Health Sciences Center at Brooklyn. Address reprint requests to the author at Box 56, 450 Clarkson Avenue, Brooklyn, NY 11203.

cell count would probably be the best measure of whether a patient's clinical course or response to treatment is likely to be affected.

Some evidence suggests an effect of HIV on concomitant sexually transmitted infections. Herpetic ulcers may not heal. Single-dose therapy for chancroid with a quinolone may not be as effective in HIV-positive as in HIV-negative patients (3). There have been reports of seronegative secondary syphilis associated with HIV (4) and of treatment failures and early central nervous system involvement in patients with concurrent syphilis and HIV (5). Both treatment failure and early neurosyphilis were reported in the pre-HIV era, and the extent to which they are more prevalent now is not clear.

Viral STDs

Viral sexually transmitted diseases such as HIV, herpes simplex virus (HSV) infection, and human papillomavirus (HPV) infection differ from easily detectable and readily treatable bacterial infections such as gonorrhea and syphilis. The viral STDs are incurable in most cases. They are lifelong infections with a long, sometimes lifelong, asymptomatic phase. Treatment is aimed at control rather than at cure.

HIV Infection

Cases of human immunodeficiency virus infection continue to increase with a case-fatality ratio that approaches 100%. Cases are occurring primarily in men and women at the peak of their productivity, most of the cases being reported in people in their thirties. Cases are concentrated in the population centers along the coasts: New York, New Jersey, Florida, and California have the most cases.

Modes of transmission are now well defined. Most cases result from sexual contact between men; heterosexual transmission in both directions; exposure to blood, by either intravenous drug use, transfusions, or occupational injuries; and perinatal exposure. The majority of cases that had been reported by the end of 1989 have been in homosexual and bisexual men. Intravenous drug users are the next largest group.

These epidemics are really separate epidemics: the epidemic in gay men, the epidemic in intravenous-drug users, and the epidemic resulting from heterosexual contact. In all of these groups, except for gay men, minorities are overrepresented, so that blacks and Hispanics comprise a percentage of cases that is higher than their representation in the population.

HIV is a classic "iceberg" disease. The clinically recognizable cases are a very small proportion of the total number of cases. The data from the San Francisco cohort of gay men indicates that people develop AIDS after a relatively long incubation period. All the evidence indicates that most individuals infected with HIV will eventually develop clinical AIDS, with a mean incubation period of over ten years.

The best predictor of the development of symptomatic disease is the absolute CD4 cell count. Once the CD4 cell count drops below 200, and particularly below 100, clinical illness is likely to develop. The majority of patients who develop *Pneumocystis carinii* pneumonia have CD4 counts below 50. There appears to be an age difference in progression to disease. Among hemophiliacs, children have become clinically ill much less rapidly than have adults.

The epidemic in gay men, in terms of transmission, began in the late 1970s; many gay men were infected by the early 1980s. Transmission in gay men substantially stopped in about 1984 as a result of changes in lifestyle and sexual behavior. Populations of gay men now show very low seroconversion rates. Although most of the cases that physicians see today are in gay men, the epidemic in gay men is over as far as transmission is concerned—an epidemic that is going to peak in the mid-1990s.

Transmission among intravenous-drug users also began in the late 1970s, but it continues among this group, although there is some evidence that the rate of infection may have slowed.

The most important HIV epidemic now is neither among gay men nor among intravenous-drug users, but is the result of heterosexual promiscuity, associated largely with "crack" cocaine and the exchange of sex for drugs and sex for money to buy drugs. Heterosexual transmission that occurs now will result in the cases of clinical AIDS that physicians will see in the late 1990s and the early part of the next century.

Serologic testing, a controversial issue a few years ago, is here to stay. The arguments that were offered against serotesting are no longer valid. The tests are very accurate. We know exactly what a positive test means. There is a lot that can be done in primary prophylaxis against tuberculosis and *Pneumocystis carinii* pneumonia and by administration of zidovudine (AZT) to delay progression to symptomatic disease.

Concern is great for the risk of exposure of health-care workers to HIV. Needlesticks are a fact of life. The risk to a health-care worker following a needlestick is about 0.4%, or one in 250.

Although seroconversions following mucous membrane exposures (splash injuries) have been reported, this form of exposure appears to be considerably less risky than a needlestick.

Herpes Simplex Virus Infection

There are two types of herpes simplex virus (HSV), type 1 and type 2. Both cause an exogenous primary infection that can be clinical or subclinical but is mainly subclinical. Both become localized in sensory ganglia. Recurrent disease occurs as a result of endogenous reactivation of the localized disease. Recurrent disease can also be either clinical or subclinical; most of it is subclinical.

Primary exogenous infection with HSV-2 is associated with constitutional symptoms, and about a three-week course. Lesions progress from vesicles to ulcers and then heal without scarring. There may be aseptic meningitis, urinary retention, and involvement of the cervix. Recurrent HSV-2 infection results from endogenous reactivation of the disease from a latent focus within sacral ganglia. Vesicles become ulcers and heal. Constitutional symptoms are not common with recurrent herpes. The whole process lasts about a week.

Two recently published papers have changed medical thinking about genital herpes. The first, a serosurvey of the population of the United States, used methods that allow clear separation of antibodies to HSV-1 and HSV-2. The researchers found that the prevalence of HSV-2-specific antibodies among the adult population of the United States was around 16% (6). These data indicate that somewhere between 15% and 20% of Americans have been infected with HSV-2, presumably carry the virus in their sacral ganglia, and are presumably at risk for asymptomatic shedding of the virus. A much smaller proportion of people actually have a history of genital herpes. This indicates the presence of a large reservoir of asymptomatic disease among individuals who do not know that they are infected.

The second paper described a group of women with specific antibodies to HSV-2 but no history of genital herpes. They were educated about the disease, were told what recurrences were like, and were asked to call the clinic or come in for an examination whenever they developed any symptoms. Eighteen of forty-three women developed clinically recognizable genital herpes during a five-month follow-up period (7). Thus, among the large group of persons who are seropositive and do not know that they have herpes, there is much disease that is totally asymptomatic, but there are also symptomatic episodes of recurrent herpes that are not recognized as such.

Isolation of the virus in tissue culture is the best method of diagnosing genital herpes simplex virus infection. Newer tests have been developed, but none of these tests are more accurate than tissue culture.

Acyclovir is the drug of choice. It comes in two forms that are useful: intravenous, which can be used for severe primary disease and for disease in compromised hosts; and oral, which can be used for primary and recurrent disease and as prophylaxis among patients who have frequent recurrences. The topical preparation is less effective than the other forms.

Patients who have herpes have three major concerns: cancer, pregnancy, and infecting sexual partners. Herpes simplex virus does not cause cervical cancer, but women who have genital herpes are at a somewhat increased risk of developing cancer of the cervix. Thus, regular cervical cytologic examinations are especially important for this group of patients.

The concern with pregnancy and the concern with infecting sexual partners arises largely from asymptomatic shedding. Studies now indicate that approximately 1% of HSV-2-infected individuals shed virus on any given day, probably through microscopic lesions, in relatively small quantities. Thus, the risk of transmission to an infant or to a sexual partner from asymptomatic shedding is not great in the individual case. However, because there are so many people who are shedding, asymptomatic shedding is responsible for upwards of half of instances of heterosexual transmission. It is also responsible for about half of the cases of neonatal herpes.

The risk of transmission from an infected pregnant woman to her child can be reduced by performing a caesarian section if the patient is symptomatic or has lesions at term. Transmission to sexual partners can be minimized by avoiding contact when lesions are present and using condoms the rest of the time.

Human Papillomavirus Infection (Genital Warts)

Knowledge of and interest in human papillomavirus (HPV) infection have tremendously increased. HPV would have been the STD of the 1980s if it had not been overshadowed by HIV. HPV is a DNA virus. It cannot be grown. There are many types, seven of which have been associated with genital infection. Types 6 and 11 cause exophytic warts, which can be diagnosed quite easily and which have low potential for malignancy. The other types tend to form flat warts that are much more difficult to diagnose and have a potential for malignant transformation. These are the types that involve the cervix. They are probably responsible for most cases of cervical cancer.

Diagnosis is by colposcopy, cytology, and histology. A variety of techniques using DNA hybridization are also used to make this diagnosis. Unfortunately, there are not yet any widely accepted diagnostic criteria. Thus, caution should be used in assigning a diagnosis of HPV infection. Optimal treatment has not been developed (8). Infection of surrounding normal tissue is usual, high failure rates are the rule, and many experts now believe that this disease is essentially incurable. One of the reasons why accurate diagnosis is so important is that the treatments are not only ineffective but involve cytotoxic agents, or destructive techniques, or both. Education and counseling of the infected patient is an important part of management.

Chancroid

According to the textbooks, infection with *Haemophilus ducreyii* results in multiple painful indurated ulcers with undermined edges. The lymph nodes are tender and may suppurate. In our STD clinic at Kings County Hospital in Brooklyn, genital ulcers nowadays are about one-third herpes, one-third chancroid, and one-third syphilis. One thing that is quite clear is that the bugs do not read the books. Clinical diagnosis is difficult even with the availability of rapid diagnostic tests. Diagnosis is not as straightforward as it used to be when the physician only had to differentiate between genital herpes and syphilis. About a third of the patients with ulcers, at least in our clinic, have more than one etiology. The combination of syphilis and chancroid is quite common, but all the other combinations and permutations also occur.

Diagnosis can be made by isolating *H. ducreyii* on special media. With appropriate microbiologic techniques, recovery rates are about 80%. Alternatively, the organisms can be visualized in gram-stained smears. Gram-negative coccobacilli form short chains. With experienced microscopists, there is good correlation between smears and cultures.

Treatment is with oral erythromycin 500 mg four times a day for a week, or with a single intramuscular injection of 250 mg of ceftriaxone. Both of these drugs work well (8). What does not work are the treatments we learned about in medical school: tetracyclines don't work anymore; sulfonamides don't work anymore. A disturbing study from Africa suggests that single-dose treatment with a quinolone (fleroxacin) is less effective in HIV-positive patients with chancroid than in HIV-negative patients (3). These data engender concern about the effectiveness of single-dose ceftriaxone for the treatment of chancroid in HIV-positive patients.

Summary

Unlike syphilis, gonorrhea, and chlamydial infection, which can cause serious short-term and long-term problems but are themselves curable, the viral STDs I have discussed are incurable and have worrisome long-term complications. The management of these illnesses should emphasize primary prevention, which involves the use of condoms and selectivity in the choice of sexual partners.

Questions and Answers

Question: Who should be screened for hepatitis B virus infection?

McCormack: At present the Centers for Disease Control recommendations are that all pregnant women should be screened (8). I agree that hepatitis screening ought to be a routine part of prenatal care. Studies have shown that screening only high-risk groups misses at least half of the positives. Identifying infected pregnant women gives an opportunity to break the chain of transmission by providing hepatitis B vaccine and hepatitis B immune globulin to the infant immediately following delivery. This is a group in which screening will produce a very important intervention.

Whether screening ought to be done more widely, I don't know. Screening to identify high-risk seronegatives who could be vaccinated would be worthwhile. For the individual who's seropositive and not pregnant, the physician cannot do a whole lot except counsel about transmission.

Question: Could you give us some insight to the incidence of congenital syphilis, at least in the New York area?

McCormack: Congenital syphilis, like the other STDs, has increased dramatically. This is another result of the "crack" cocaine epidemic. Unlike intravenous drugs, which are primarily used by men, "crack" is at least equally attractive to women.

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Syphilis: From Beethoven to HIV

EDMUND C. TRAMONT, MD

SYPHILIS has played a pivotal role in modern history. The ravaging effect of late syphilis on the minds of the powerful and famous who were afflicted with syphilis is, of course, speculative, but that the disease influenced at least some of their actions is unquestioned. There is credible evidence that Henry VIII, Sir Randolph Churchill, Ivan the Terrible, Catherine the Great, Ludwig Beethoven, Franz Schubert, John Keats, Napoleon Bonaparte, Peter the Great, Florence Nightingale, and Al Capone, among others, suffered cerebral damage due to syphilis. Would Winston Churchill have been so driven had he not felt compelled to revive and restore his father's name? Would Russia's history been altered had Ivan the Terrible remained benevolent? Would Great Britain have remained Catholic if Henry VIII had been more faithful? And what musical treasure was the world denied because of Beethoven's syphilis-induced deafness?

The prevalence of syphilis before the advent of penicillin is instructive. The germ theory, which is barely a century old, set the stage for antibody testing. The first serologic tests for syphilis were developed in the early 20th century. One of the earliest tests was developed by the famed Harvard pathologist Homer Smith. However, when he set out to determine the limits of his new discovery by testing consecutive admissions to the Massachusetts General Hospital, Smith felt that the high prevalence (15%–20%) would not be accepted by the Brahmins of Boston. A few years later, Wassermann developed a similar test (based on the nonspecific reaginic reaction) and prevalence surveys were undertaken throughout the Western world (Table 1).

It was because of the high prevalence rate in New York City that The Mount Sinai Hospital instituted hospital admission screening. And it was this experience which heralded the institution of routine hospital admission screening as standard practice championed by the then surgeon general, Dr. Thomas Parran (1).

The introduction of penicillin and other effective antibiotics, coupled with the established public health measure of contact tracing, resulted in effective epidemiologic treatment that dramatically reduced the incidence of new cases to its nadir by 1956 (Fig. 1). However, as public health priorities shifted to other sexually transmitted diseases, the incidence swiftly increased to a baseline or endemic level, which remained relatively stable over the next 25 years. However, since 1986, there has been an alarming increase in new cases (Fig. 1).

Although the reason for this resurgence is not precisely known, it is most likely multifactorial. The coincident human immunodeficiency virus (HIV) epidemic undoubtedly plays an important role: persons doubly infected tend to suffer more severe disease secondary to immunologic dysfunction, resulting in higher treponemal levels, and, hence, are also more infectious to their partners (2).

The high prevalence of drug abuse among the young in the U.S. population—especially addiction to crack cocaine—is also playing a role. Not only are addicted prostitutes more likely to increase the spread of syphilis and other sexually

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The view of the author does not purport to reflect the position of the Department of the Army or the Department of Defense. The author is Professor of Medicine, Uniformed Services University of Health Sciences Medical School, Bethesda, MD, and Associate Director for HIV and Program Director of the Military Medical Consortium for Applied Retroviral Research, Walter Reed Army Medical Center, Washington, D.C.

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transmitted diseases, but the reluctance of public health officials to risk bodily harm to undertake meaningful contact tracing among those using crack cocaine undermines this time-proven, effective control measure.

Finally, the AIDS epidemic has required further shifting of public health priorities. However, since the incidence in general of other sexually transmitted diseases has decreased, the resurgence of syphilis must be due to other complicating factors.

The increased use of spectinomycin, which has no activity against *Treponema pallidum*, as treatment for penicillinase–producing *Neisseria gonorrhoeae* (PPNG) appears to have played only a minor, if any, role. Unlike many other human bacteria, *T. pallidum* has not shown an increase in antibiotic resistance.

In summary, syphilis has undoubtedly affected modern history and, despite continuing success with antibiotic therapy, is presently increasing in incidence.

Pathogenesis

The pathogenesis of syphilis has been understood and appreciated for many years (2). Soon after contact, spirochetemia develops, infecting every organ (Fig. 2). The walls of arterioles and other small vessels of these organs are preferentially infected, resulting in a characteristic endarteritis (Fig. 3). An immune response is slow to develop. Its effectiveness in controlling the infection is dependent primarily on the state of the host's cellular immune system. Hence, any process that dampens the cellular arm of the immune system, such as undernourishment or HIV infection, encourages the development of florid cases of secondary syphilis and late complications (tertiary syphilis).

In order to clinically classify syphilis, clinicians have long divided the course of syphilis into primary (chancre), secondary, early latent, late latent, and tertiary syphilis (Fig. 4). Although these distinctions correlate in general with the pathogenesis, it must be emphasized that a great deal of overlap occurs, and the dynamism involved with syphilitic infections renders these classifications relatively inadequate as a guide to treatment (see below).

Primary syphilis refers to the presence of a chancre, a relatively painless, shallow-based single ulcer, teeming with spirochetes, developing wherever the inoculation happens to occur. Painless to minimally painful regional lymphadenopathy usually accompanies the chancre. It disappears with the initiation of the host's immune response.

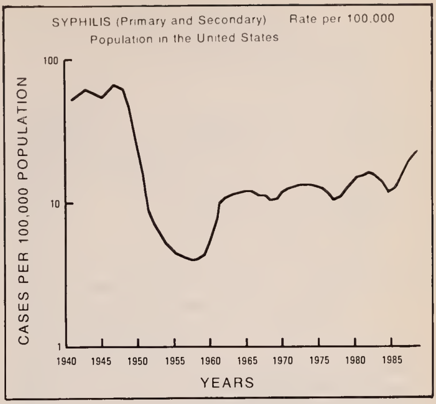

Fig. 1. Rate of primary and secondary syphilis per 100,000 population in the United States. Data from Centers for Disease Control.

Secondary syphilis refers to the myriad of signs and symptoms coinciding with the highest antigenic load of *T. pallidum* and the height of the host's immune response (Table 2). If the host is capable of mounting a vigorous response, he or she is likely to rid themselves of the infection, except in protected or privileged sites such as the eye or the inner ear. Obviously, individuals who are immunosuppressed for whatever reason—malnourishment, concomitant infection with HIV or with TB, late pregnancy—are unlikely to mount an effective immune response, setting the stage for either prolonged illness or end-organ damage, or both. It is during the primary and secondary stages that the chance of person-to-person transmission is greatest.

Early latent syphilis refers to that period in which secondary relapses with spirochetemia might occur, up to 4 years. This distinction is par-

TABLE 1

Prevalence of Syphilis in the Preantibiotic Era

Year	City	Percent
1907	Boston	15–20
1914	London Paris Berlin	12–15
1917–1941	Connecticut (autopsy)	9.7
1935	New York (The Mount Sinai Hospital)	8

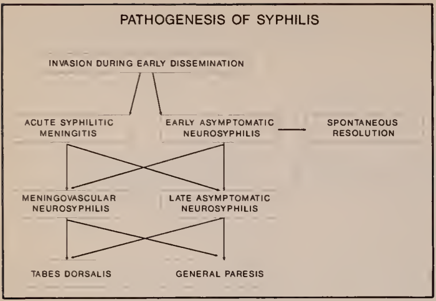
PATHOGENESIS OF SYPHILIS
INVASION DURING EARLY DISSEMINATION
ACUTE SYPHILITIC MENINGITIS
EARLY ASYMPTOMATIC NEUROSYPHILIS
SPONTANEOUS RESOLUTION
MENINGOVASCULAR NEUROSYPHILIS
LATE ASYMPTOMATIC NEUROSYPHILIS
TABES DORSALIS
GENERAL PARESIS

Fig. 2. Pathogenesis of syphilis.

ticularly important in determining the risk of transmission to the fetus.

Late latent syphilis refers to the period of latency before tertiary or end-organ damage (late syphilis) occurs.

Tertiary or late syphilis refers to end-organ damage due to the effects of endarteritis obliterans (ischemia) and, on occasion, direct tissue invasion. Three forms of tertiary syphilis are recognized: neurosyphilis (4%–23% of cases), cardiovascular syphilis (22%–83%) and benign gummatous syphilis (5%–10%). The latter two are rare in the antibiotic era; the former is more common, due primarily to the fact that the immune system is less efficient in the central nervous system, and antibiotics generally penetrate poorly into that system.

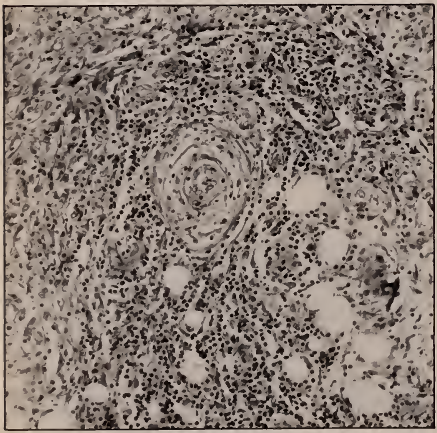

Fig. 3. Endarteritis obliterans.

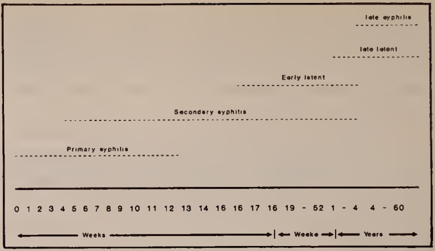

Fig. 4. Duration of stages of syphilis.

Neurosyphilis has been divided into two forms based primarily on pathologic changes described during the preantibiotic era: meningovascular neurosyphilis (endarteritis obliterans, 24%–29% of cases) and parenchymal neurosyphilis (direct tissue invasion, 43%–52% of cases) (3). However, a combination of the two forms is almost invariably present. The clinical manifestations can be quite varied, ranging from stroke to mental changes, aptly described by the mnemonic PARESIS (Table 3).

Misdiagnosis

In the preantibiotic era, Sir William Osler placed syphilis at the heart of clinical medicine: "Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you." Antibiotics have relegated syphilis to the back burner of modern medicine, the legacy of which is misdiagnosis, often resulting in mistreatment (2). Among the misdiagnoses:

- rectal chancre mistaken for abscess, rectal fistula, hemorrhoids, rectal cancer, lymphoma;
- tongue chancre mistaken for cancer of the tongue;
- chancre mistaken for incarcerated hernia;
- secondary syphilis mistaken for Menière's syndrome, hepatitis, carcinomatous meningitis, intracranial neoplasm;
- optic neuritis mistaken for multiple sclerosis.

Diagnosis

The laboratory diagnosis of syphilis has not changed for nearly one hundred years and encompasses dark-field microscopy and serology. Although the treponemas can be demonstrated directly by dark-field microscopy or direct antibody-targeted staining, such as direct fluorescence, isolation requires live animal inoculation and, hence, remains a research tool.

TABLE 2

Clinical Manifestations of Secondary Syphilis

Genital 20%–25%
chancre
condyloma lata
mucous patches

Skin 85%–90%
rash
  macular
  macular papular
  papular
  pustular
generalized lymphadenopathy
pruritus

Mouth and Throat 30%–35%
mucous patches
ulcers
pharyngitis
laryngitis

Constitutional Symptoms 65%–70%
fever
malaise
anorexia
weightloss
arthralgias

Central Nervous System 8%–40%
Asymptomatic 8%–33%
Symptomatic 1%–2%
  headache
  meningismus
  meningitis
  ocular
    diplopia
    decreased vision
  otitic
    tinnitus
    vertigo
  cranial nerve II–VIII

Renal Rare*
glomerulonephritis
nephrotic syndrome

Gastrointestinal Rare
intestinal wall invasion

Arthritis and periostitis Rare

Hepatitis

* Actual incidence not known.

TABLE 3

Signs and Symptoms of General Paresis

P	Personality	Irritability, emotional liability (agitation, euphoria, depression), paranoia
A	Affect	Carelessness of appearance, apathy, expressionless facies, inappropriate behavior
R	Reflex	Abnormal reflexes (usually hyperactive), tremors of tongue, hand, face
E	Eye	Pupillary abnormalities, especially Argyll-Robertson pupils
S	Sensorium	Illusions, hallucinations, delusions of grandeur
I	Intellect	Memory loss, impaired capacity to learn, lack of insight, confusion, disorientation
S	Speech	Slurred speech

Other signs and symptoms referable to endarteritis and focal infarcts are usually also present, i.e., seizures.

Nontreponemal and treponemal serologic testing continues to be the cornerstone of laboratory diagnosis (Table 4). Nonspecific reagin tests (VDRL, RPR, ART) are inexpensive, sensitive, and easy to perform, thus meeting the criteria for screening tests. They have the added benefit of usefulness in monitoring treatment.

TABLE 4

Percentage of Patients with Positive Responses to Commonly Used Serologic Tests

Test	Stage 1°	2°	Late
Nontreponemal (reaginic tests)			
Venereal Disease Research Laboratory (Reaginic) test (VDRL)	70*	99*	1†
Rapid plasma reagin card test (RPR)	80	99	0
Automated reagin test (ART)			
Specific treponemal tests			
Fluorescent antibody absorbed test (FTA-ABS)	85	100	98
T. pallidum hemagglutination assay (TPHA, MHA-TP)	65	100	95
Treponemal immobilization test (TPI)	50	97	95

* Percentage of patients with positive serologic tests in treated or untreated primary or secondary syphilis.
† Treated late syphilis.

TABLE 5

Treatment of Syphilis, All Stages, Recommendations of Edmund C. Tramont, M.D.

Amoxicillin, 3 g po plus probenicid, 0.5 g po, bid × 14 days
Acqueous PCN G, 3M units IV, q6h × 10 days
Doxycycline, 200 mg po, bid × 21 days
Procaine PCN, 2.4M units IM, plus probenicid, 0.5 g po, qd × 10 days
Ceftriaxone, 1.0 g IM, qd × 5–14 days
Benzathine PCN, 2.4M units IM, q weekly × 3 doses plus doxycycline, 200 mg po, bid × 21 days or amoxicillin, 3 g po, plus 0.5 g probenicid po, bid × 14 days

Pregnant women should be treated as nonpregnant women, except for the use of doxycycline.

Neurosyphilis

The challenge for modern-day clinicians is diagnosing and treating neurosyphilis, the development of which is a clinical mistake. The CNS is invaded in at least 40% of cases of early syphilis (4), and in a small but significant number of patients, late manifestations occur 15–25 years later (Table 2) (5). For example, a person with inadequately treated neurosyphilis is twice as likely to have cerebral vascular injury, compared to others with neurologic disease. As noted above, the determinant in the development of neurosyphilis appears to be the state of the host's cellular immune system. Furthermore, the clinical manifestations may be subtle and altered by antibiotics.

The cerebrospinal fluid formula is nondiag-

TABLE 6
Clinical Presentation of Neurosyphilis in Preantibiotic, Postantibiotic, and AIDS Era

	1932–1942		1965–1980		1985–1990	
	No. pts	%	No. pts	%	No. pts	%
Asymptomatic	219	28	123	37	23	46
Symptomatic		72		63		54
seizures	4	1	59	28	22	44
meningovascular	103	18	42	20	11	
dementia (paresis)	203	35	26	12	1	
tabes dorsalis	203	35	9	4		
myelopathy	19	4	10	5	1	
neuroophthalmologic	20	4	56	26	8	
hearing loss	9	2	4	2	1	
other	6	1	6	3	1	
Total	563		212		50	

nostic; cerebrospinal fluid findings in late neurosyphilis are as follows:

protein	
45	61%
45–100	34%
>100	5%
cells (predominantly mononuclear)	
5	18%
5–10	70%
>10	12%
glucose: within normal limits	

However, the demonstration of local CNS production of antibodies is diagnostic (2), including the demonstration of specific IgM to *T. pallidum.*

Treatment

The two principles of treatment for neurosyphilis are, first, give enough antibiotic (since the organism has remained quite sensitive to antibiotic treatment) (5), and second, treat all patients as if they have neurosyphilis (since 40% have evidence of CNS invasion) (6). Treatment regimens are shown in Table 5; alternatively, the patient may be treated with 2.4 million units of benzathine penicillin every week for 3 weeks and followed closely with periodic evaluations of cerebrospinal fluid for normalization of all parameters.

All patients, no matter what therapy they receive, should be tested for nontreponemal serologic status over time. The titer should drop more than fourfold after 3 months, or more than eightfold after 6 months.

Alternatively, patients with early manifestations of syphilis should test VDRL (RPR) negative after 24 months, patients with late manifestations, after 60 months.

Syphilis in the AIDS Era

Dual infection with HIV and *T. pallidum* is common and should be expected. Because of the ensuing prominent defect in cellular immunity, the syphilis in dually infected patients may be more malignant (Table 6) (7). Beause of the dysfunction of the immune system, serologic tests cannot be relied on either for diagnosis or to track the adequacy of treatment, and special stains of biopsied materials may be required to establish the diagnosis (8). Treatment should always be at levels adequate to treat neurosyphilis.

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Gonorrhea

EDWARD W. HOOK III, M.D.

ONE of the first diseases brought to mind by the term "venereal diseases," or "VD," or the more current term "sexually transmitted diseases," is gonorrhea, which is among the oldest known of the group. As one or another of these diseases comes under epidemiologic or prophylactic control, the spectrum of these diseases seems to expand; they come and go, ebb and flow, as time goes on. The traditional entree to discussions of one of the sexually transmitted diseases is to declare that the disease is increasing dramatically, is reaching the highest number of persons in years, and poses a terrible public health problem. Yet the rate for gonorrhea, although remaining an important public health problem, has in fact in the last 10 to 15 years levelled out, then slowly begun to decline.

The peak number of reported cases of gonorrhea in the United States occurred in 1976, when about 1,100,000 cases were reported. Because underreporting is so common, I suspect that there were over two and a half million cases of gonorrhea in the United States that year. After 1976, gonorrhea rates levelled out, for a combination of different reasons. The decline early in the 1980s has been attributed in large part to changes in behavior by homosexually active men, who prior to those years carried the burden and numerically provided a large percentage of the total number of cases of gonorrhea. In the early 1980s, because of the HIV epidemic, this group of men began to change their sexual behavior.

But even more recently, gonorrhea rates have continued to decline, for multiple reasons. One of the most important of these is that condom use has increased, as McCormack has shown. The only major change in heterosexual behavior that is presently occurring among college students in the United States is that they are using more condoms. They do not have fewer partners, they are not having less sex, but they are using more condoms; and even intermittent condom use does contribute to decreasing rates of STDs, especially of gonorrhea.

Despite these declines, gonorrhea is still a common disease. In 1990 about 650,000 cases of gonorrhea will be reported in the United States, representing a true incidence of about one and a quarter million cases of gonorrhea for the American populace. In addition, as gonorrhea rates decline, we are discovering that the epidemiology of the disease is changing.

The Importance of Core Groups. In studying sexually transmitted diseases (STDs) in general, the theoretical construct "core groups" is essential to understanding why STDs remain present in the population. Sustaining or changing the endemnicity of STDs is a function of the disproportionate contribution to disease rates of such groups, which can be defined by a number of different descriptors: age, sex, race, sex preference, sexual behavior, health-care-seeking behaviors, and so forth.

For instance, prior to the HIV epidemic, homosexually active men were responsible for a disproportionate amount of syphilis and gonorrhea and the other STDs that were occurring in the United States. For diseases like gonorrhea and chlamydial infections, part of the core group is comprised of young adolescent women. In the United States the highest rates of gonorrhea and of chlamydial infection occur in teenage females; blacks in particular have a higher burden of most STDs. For example, gonorrhea rates for blacks are five- to ten-fold that of whites; syphilis rates are almost 40 times that of whites. So individuals

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Adapted from the author's presentation at the seminar Sexually Transmitted Diseases, held at The Mount Sinai Medical Center on March 23, 1990. From the Division of Infectious Diseases, Johns Hopkins Hospital, Baltimore, MD. Address reprint requests to the author at Blalock Building, Room 1111, 600 North Wolfe Street, Baltimore, MD 21205.

in these core groups are responsible for a disproportionate amount of the disease.

In addition, rates are affected by interactions between core-group members and non-core-group individuals. For instance, an intravenous-drug user, who would be a member of a core group for certain sexually transmitted diseases, can have sexual partners who are not intravenous drug users and thus further contribute to the STD burden in the community.

In the last decade, gonorrhea rates have decreased, but at the same time, because of the ongoing epidemic of drug use, the relative size of the core group and the absolute size of the core group have increased, so that although the overall number of cases of gonorrhea reported in the United States is less today than it was in 1980, the core group—the individuals who are hardest to reach, who are hardest to take care of, who are the driving force sustaining the disease, and who are the biggest barrier to eradication—has actually increased in size. As a result, it is going to become increasingly difficult to maintain the decline in gonorrhea rates in the United States.

Who are core group transmitters? For gonorrhea in particular, a number of different groups contribute. Early on, this group of individuals was thought to be a very important contributor to the continuance of gonococcal epidemiology in communities. It is estimated that about 1% of sexually active men in the population were asymptomatically infected with *N. gonorrhoeae,* which translates to gonorrhea in between 5% and 10% of all men. Among women carriers of *N. gonorrhoeae,* a larger proportion than among men were asymptomatic. The assumption is that an individual who is asymptomatic would not seek health care and would therefore be more likely to continue spreading the disease. Such persons certainly do contribute to and are part of the core group, but the core group is much more complex than was previously thought.

Another core group consists of prostitutes and high-frequency transmitters, that is, individuals who have large numbers of sexual partners and, as a result of infection, disproportionately cause large numbers of cases.

Repeaters—individuals who are regulars in STD clinics, who contract two, three, and four cases of gonorrhea a year, who have multiple episodes of syphilis and other STDs, who, for whatever reason, practice a whole constellation of high-risk behaviors—are an important target group for behavioral intervention, which is integral in the management of STDs and HIV transmission.

More recently, two other groups have been added to our constellation of core group transmitters: symptomatic individuals who fail to stop having sex despite the presence of symptoms, and asymptomatic persons notified that they have recently been exposed to an individual with an STD. We have recently shown that about a quarter of men and about a third of women who are either symptomatic, or have been notified that they have recently been exposed to an individual with gonorrhea, continue to be sexually active between the date of notification and the onset of symptoms. Such individuals are highly likely to transmit their infections.

Access to Health Care. Finally, changes in access to health care are going to continue to affect the ability to control diseases. STDs in general, whether the new wave of the HIV epidemic, the syphilis epidemic, or the gonococcal epidemic, are diseases predominantly of lower socioeconomic classes, whose members have limited access to health care. As a result of limited access, those individuals are more likely to continue transmitting disease. The core group is thus one important part of and a reflection of the present changing epidemiology of gonorrhea in the United States, including the transmission and propagation of antimicrobial-resistant *N. gonorrhoeae.*

Approaches to Treatment

There is a long and glorious history of different approaches to treating STDs, but the one that probably gave the patient the most fun was Dr. Reed's Eureka Tonic. It was great stuff; it not only cured syphilorrhea but it strengthened your constitution and inspired ambition, grit, get-up, nerve, courage, thrills, stamina, vim, vigor, vitality; it even infused new life into weak, run-down, discouraged folks in a short time. Dr. Reed's formulation probably did do all that because it was a dilute solution of cocaine in alcohol. Whether or not it cured syphilorrhea remains speculative.

Urologists, who treated most patients with gonorrhea before the advent of modern antimicrobials, used irrigative therapy to manage gonococcal infections. They would insert a probelike instrument into the male urethra or into the female cervix and then irrigate the potential site of infection with a variety of caustic agents, including potassium permanganate. This description may be found in an old text entitled *Gonococcic Urethritis in the Male,* which details three different heights irrigated, depending on the anatomic site of involvement.

The advent of penicillin was thought to be a threshold and the major mechanism in the treatment of gonorrhea. It was so important that it could be advertised on every street corner and—the year was 1944—posters for it got higher billing than "Thrash the Axis."

In fact, penicillin therapy came after the advent of antimicrobial therapy for gonorrhea. In 1937, sulfanilimide, the first of the sulfonamides, was used to treat gonorrhea with great success. Unfortunately, between 1937 and 1944 the gonococcus gradually developed resistance to sulfonamide therapies, to the point that the dose could no longer be increased to ensure a cure. As a result, in 1944 over a third of patients with gonorrhea failed to be cured with sulfonamides. Fortunately, the year before, Mahoney and his co-workers, using only 160,000 units of penicillin, were able to treat gonorrhea successfully.

The problem with sulfonamides illustrates in a shorter and more compressed time period what has happened with betalactam antibiotics since 1944, when Mahoney and his co-workers first used penicillin. The gonococcus has become increasingly resistant to the antibiotics used for therapy. Thus between 1943 and 1972, failure rates increased and, as a consequence, the recommended dosage of penicillin was also repeatedly increased, because there is such a large therapeutic toxic ratio for penicillins. In 1972, the peak was reached—4.8 million units of penicillin was recommended and, with the addition of probenicin to delay excretion of the antibiotic, we gained about another 10 years for penicillin therapy. This is an important level, however, because to increase dosage again to 7.2 million units would increase the frequency of procaine reactions from about 0.1% to 10% of individuals.

In 1976 plasmid-mediated, penicillinase-producing *Neisseria gonorrhoeae* (PPNG) were documented, having originated or having been discovered in two different geographic locales, Africa and Southeast Asia. McCormack, in an editorial in the *New England Journal of Medicine,* stated that PPNG represented the death knell of the utility of penicillin for treating gonorrhea. That has certainly proved to be the case because in 1984, Sparling and his coworkers described an outbreak of high-level chromosomally mediated penicillin resistance. This form of resistance is different from the plasmid-mediated form because it is not easily detectable with simple laboratory tests.

In 1987, Tramont and coworkers described an outbreak of gonorrhea among military men serving in Korea caused by a strain of *N. gonorrhoeae* with high-level resistance to spectinomycin, an aminoglycoside.

The culmination of events such as these was a revision of the guidelines for treatment of STDs from the Centers for Disease Control (CDC) in 1989; for the first time in almost 50 years, penicillin was no longer the drug of choice for gonorrhea. The abolition of penicillin therapy has an immense impact on public health because of the alternatives: first, we have to learn about new drugs; second, the alternatives are more expensive than penicillin; and third, we have yet to see all the effects of this changing recommendation.

Resistance due to plasmid-mediated beta lactamase production is relatively easy to detect. This plasmid, which can be transmitted from one gonococcus to another or from one bacterium to another, has the capacity to spread from strain to strain relatively quickly. It also results in single-step changes in high-level resistance such that a plasmidless organism sensitive to penicillin becomes almost impervious to penicillin with the acquisition of the plasmid.

In the United States from 1976 through about 1979, only a few hundred cases of gonorrhea due to PPNG occurred each year, and throughout this time most of the people who had these infections acquired them because they either had sex with somebody who traveled outside of the country, or traveled abroad themselves. In 1979, however, the PPNG strains of gonococci seemed to enter the general population, and since that time they have steadily spread throughout the nation, so much so that in 1989, 4½% of all cases of gonorrhea in the United States were caused by PPNG.

In addition, geographic heterogeneity persists in this form of gonococcal resistance. There are some cities, such as New York or Miami or Los Angeles, in which PPNG is very common, comprising 10% or 15% of all cases; there are other cities, such as cities in the Midwest, in which PPNG still represents less than 1% of all cases.

Chromosomally mediated resistance, however, is not limited to penicillin, but can include resistance to a large number of different antibiotics. Chromosomal mutations, such as Pen-A, Pen-B, MPR, and Tem, all seem to affect and encode for small increases in the resistance of gonococci to penicillins. Unfortunately, they all work by different mechanisms, and as a result there is no simple, easy test for detecting these forms of resistance. We cannot test for a single enzyme such as beta lactamase. Some of these enzymes affect penicillin-binding proteins or cell-wall permeability. Additionally, these mechanisms of resistance are relatively nonspecific and affect not only penicillin resistance, but also the susceptibility of these organisms to tetracycline, the cephalosporins, erythromycin, spectinomycin, and other aminoglycosides.

Chromosomally mediated resistance results in a gradual stepwise increase in resistance, and along with that, gradual changes in failure rates. Changes in the percentage of patients failing therapy according to the minimum inhibitory concentration of the organism indicate that a mutation which causes a relatively small change in the susceptibility of the organism also causes a relatively small change in the failure rates. As a result, this gradual process, this accretion of chromosomal mutations, will result in gradually increasing failure rates, until finally it dawns on somebody that many more patients are failing therapy than did before.

Antibiotic Use as Driving Force for Resistance. The driving force for resistance appears to be, amongst other things, antibiotic use. The proportion of gonococcal isolates with two different forms of antibiotic resistance seen in American military men in Korea between 1980 and 1985 is a case in point. In 1980, when penicillin was the drug of choice for treating gonorrhea, PPNG organisms were not a problem. Penicillin was widely used, sooner or later PPNG organisms were introduced into the population, and, driven by penicillin use, the proportion of PPNG organisms increased dramatically over a year and a half from zero to more than 40% of all isolates. After this change had been detected and appreciated, the military adopted a new therapy, spectinomycin, and two things happened: first, without the driving force of penicillin usage to perpetuate antimicrobial resistance, the proportion of PPNG isolates declined dramatically; second, somewhat later, the number of cases of spectinomycin-resistant organisms increased, driven by the current drug of choice.

Thus we have to expect that whatever drugs we use in the community, whether for the treatment of gonorrhea or for other diseases, are going to lead to increasing antibiotic resistance.

To deal with these problems in the United States, the CDC recently created the Gonococcal Isolates Surveillance System, in which four sentinel laboratories collected specimens from a total of 21 cities across the United States to monitor antimicrobial susceptibility. This system was created because of the failure of the previous research, based on the assumption that we could monitor the easy-to-detect form of beta-lactamase-induced resistance, and that chromosomal resistance would parallel beta-lactamase-induced resistance. That assumption of parallelism turned out to be false. If the assumption did hold, cities which have high levels of PPNG could be expected to have high levels of strains with chromosomal resistance. That did not occur. In some cities in which PPNG was relatively common, there were relatively few chromosomally resistant isolates; in some cities that had no PPNG, there were relatively high proportions of strains with chromosomally mediated resistance. So the Gonococcal Isolates Surveillance System was created. One result has been the recent change in recommendations for treating gonorrhea.

Experience in Baltimore. In Baltimore we recently had the opportunity through the Surveillance Program to study 150 isolates for the development of antibiotic resistance. We found that 15% of our isolates had high-level tetracycline resistance and the rest were sensitive. Over the next couple of years, strains were isolated that showed chromosomally mediated penicillin resistance rising from zero to 21% and stabilizing at 20% to 25%. This occurrence was accompanied by a gradual increase in PPNG as well.

At the time these increases were occurring, we also performed another study in our STD clinics looking at antimicrobial resistance. At the outset of the study, strains with high-level tetracycline resistance were already widespread in the community, and there were a few strains with chromosomal-derived resistance. When chromosomal resistance appeared, it appeared in multiple strains of gonococci at the same time, suggesting that this was an evolutionary process, not a process by which resistant organisms were imported into the community.

We then followed up patients with these strains to look at risk factors for development of chromosomal resistance. We studied 126 men with gonorrhea, of whom 22 were infected with high-level tetracycline-resistant strains (the endemic form of antibiotic resistance), 17 with chromosomally mediated penicillin resistance, and the other 87 with sensitive isolates.

This emerging form of resistance had a number of distinctive characteristics. The individuals infected with such strains tended to be older, to have had more lifetime sexual partners, and to have had more sexual partners in the last 30 days; and each had a history of a prior STD. This is our core group of transmitters, and it is this core group that is now not only sustaining gonorrhea in the community, but also contributing to the development of resistant strains in the community. We were further able to document that the people with chromosomally resistant strains had traveled outside the community, were more likely to be intravenous drug users, and were more likely to have utilized the services of prostitutes than the people with strains showing either tetracycline resistance or other antibiotic resistance.

We further found that almost 10% of men and women attending the STD clinic had taken antibiotics in the last two weeks, usually because they thought they had sexually transmitted disease, and that the antibiotics they were taking were predominantly penicillins and tetracyclines, drugs to which resistance was emerging. Additionally, as we know, antibiotic compliance is not complete; when symptoms abate, individuals stop taking their medications and, as a result, the major source of antibiotics for these individuals was from supplies sitting around at home from a prior episode of illness. Furthermore, a quarter of the men who have used antibiotics were able to purchase them without prescriptions. And about 7% of men had received their antibiotics from a friend or sexual partner as well. So there is a lot of antibiotic use. Unfortunately the antibiotics to which resistance is developing are the ones taken for suspected sexually transmitted diseases.

In 1989, STD treatment guidelines were changed, and ceftriaxone plus doxycycline were the drugs of choice for treating gonorrhea. Ceftriaxone is a very active agent and we in Baltimore had an opportunity to repeat Tramont's observations. In Baltimore, strains with high-level tetracycline resistance were very common, and chromosomally mediated penicillin resistance was developing, along with steadily increasing PPNG. At this time, relatively little ceftriaxone was used to treat the sexually transmitted diseases.

In November 1988 we began prescribing more and more ceftriaxone; as a result, in the first full six-month period we found a substantial decrease in the proportion of gonococcal isolates resistant to antibiotics. This again indicates that the CDC made the right choice recommending a change to ceftriaxone. An expected result of that change is a diminution in resistant strains of *N. gonorrhoeae* for a while. I have no doubt, however, that resistant strains will recur, gradually and over time, because of the use of the new antibiotic.

Reasons for Failure of Treatment. Finally, there are several reasons for gonococcal treatment failures:

- reacquisition of disease, that is, reexposure to an untreated sex partner. Referral of sex partners is an essential part of controlling STDs. Reexposure to untreated partners is the major cause for apparent—and I emphasize the word apparent—treatment failures.
- inadequate treatment—either the wrong choice of therapeutic agent (for example, ampicillin or penicillin), or poor compliance in multiple-dose therapy, or self-treatment.
- resistance to antibiotic agents.

Clinically, then, we need to continue counseling our patients not only to hear no evil, see no evil, and speak no evil but—once they are adolescents—also to start spreading no evil. Counseling is an important part of what we do in our efforts to control gonorrhea.

Questions and Answers

Edward Bottone: What would you tell us to do in the clinical laboratory to identify resistant strains?

Hook: One approach would be to periodically subject gonococcal isolates to antimicrobial susceptibility testing. The alternative would be to either encourage the CDC, or to go with what they've already done in the antimicrobial surveillance system, in monitoring antibiotic sensitivity. I think there is a real need for monitoring antimicrobial susceptibility so that the physician can choose and recommend therapies which will be effective without having to wait for sensitivity testing. That approach is different from what we use in the hospital for patients with pneumonias and nosocomial infections. The question as to whether you feel that you need to have your own surveillance system locally or whether you're willing to wait for the CDC's results from their 21 cities is a personal choice that only laboratory directors such as yourself can make.

Question: Why are the gonorrhea and syphilis rates going in opposing directions?

Hook: That's a very good question, and I don't have the whole answer to it. My own personal bias is that part of the reason we have opposing trends in gonorrhea and syphilis is that, first of all, condom use has indeed increased, and we in Baltimore have data in press showing that even intermittent condom use certainly does result in decreased risk for transmission of gonorrhea. We don't know if that's the case for syphilis.

A second factor which perhaps needs to be considered is that syphilis and other genital ulcer diseases like herpes and perhaps even chancroid are diseases in which intromission is not necessarily essential for transmission of the disease. Simple contact can transmit. As a result, those are diseases that can potentially be transmitted during foreplay before somebody puts on the condom that prevents them from transmitting gonorrhea.

Third, a numerical issue. Gonorrhea has decreased dramatically, and as I mentioned, in 1990 we will be faced with only about 600,000 reported cases. On the other hand, syphilis is increasing dramatically; for the first time in a long time, in 1990 we'll have more than 60,000 cases. So that syphilis is a much rarer disease, and when it's concentrated in that core group of individuals—the drug users, the crack users, the prostitutes, the medically disadvantaged—it's going to stay there. Those people are going to have a lot of disease and they are not necessarily going to be spreading it to other parts of the community.

I don't think this answer is even the whole answer, but I think each element is part of the reason for this differential trend. It's a tough question, and if somebody could really answer it well and completely, it would be a great contribution.

Question: How accurate are figures on gonorrhea incidence?

Hook: Studies we've just recently completed in Baltimore suggest that the epidemiologic characteristics of gonorrhea are those of an incident disease. That is, individuals seek therapy and are diagnosed relatively shortly after they acquire the microorganism and become symptomatic. That may be very different from a disease like chlamydia, which in my mind (my supposition is supported by our data in Baltimore) may be a prevalent disease, because the symptoms are less obvious, and persons with only mild symptoms can have it and transmit it over long periods of time. So the background prevalence of chlamydia is probably relatively higher in a population than gonorrhea. But I think that our figures probably do represent the incident infections. As I mentioned, the CDC seems to think that the number of reported cases reflects between 40% and 50% of all cases that are actually being seen and treated.

Chlamydia

Max A. Chernesky, Ph.D.

I discuss here the characteristics and epidemiology of *Chlamydia,* dealing with infections first in men, then in women, and finally in children, and discussing also both treatment and diagnosis.

Characteristics of the Organisms. These gram-negative bacteria have many characteristics of viruses in that they are obligate intracellular organisms, and therefore the technology required in the laboratory is cell culture. Two specific antigens are usually in abundance both on the organism and in secretions. These are the major outer membrane proteins (MOMP) and the lipopolysaccharide (LPS). Unlike viruses, *Chlamydia* are susceptible to antibiotics. In current classification, there are three species: *C. trachomatis, C. psittaci,* and the new TWAR strain, now called *C. pneumoniae*. There are 15 serovars of *C. trachomatis.* The A-B-C complex comprises the organisms that cause trachoma; the L1, 2, and 3 serovars cause lymphogranuloma venereum; and the D to K group have been found to cause many of the sexually transmitted diseases, as well as inclusion conjunctivitis in both adults and children. And of course, in the newborn, pneumonia is a major problem.

Pathogenesis. The entire life cycle of *C. trachomatis* (Fig. 1) is completed in about 48 hours and involves inclusion formation and cell lysis. Treatment of cells in culture with cyclohexamide prevents lysis, allowing the appearance of the inclusion. During the process, a great deal of glycogen surrounds the inclusion, which takes up iodine used to stain the tissue culture. Antigens are also expressed and immunofluorescent stains also indicate inclusions.

In the natural history of disease, the cervix plays a central role in infection (Fig. 2).

Infections in Males. Although infection can take place in the conjunctiva, the urethra is really the focus for infection, either with or without *Neisseria gonorrhoeae* (Table 1). A watery discharge is present in patients with symptoms of *Chlamydia* infection. If ascending infection occurs, epididymitis, prostatitis, or Reiter's syndrome may be complications of infection. Male infertility is a possible complication, but more studies are needed to establish a strong association of *C. trachomatis* infection with male infertility.

Young, sexually active men are most often infected. Among the clinical characteristics differentiating gonococcal and nongonococcal (chlamydial) urethritis (Table 2) are a much longer incubation period for the chlamydial form. The onset is gradual and dysuria is often absent. The urethral discharge is quite different in the two diseases, as reflected by fewer pus cells present in *Chlamydia*-induced discharge. Recent findings indicate that asymptomatic carriage of *C. trachomatis* organisms in the male urethra is not uncommon.

Infections in Women. Clinical manifestations of infection in the female lower genital tract are cervicitis and urethritis (Table 1). Ascending infection can lead to endometritis, salpingitis, pelvic inflammatory disease, perihepatitis, ectopic pregnancy, and infertility. In Hamilton, Canada, in birth control clinics, 55% of women infected were less than 20 years old and another 37% were between 20 and 30 years old (Table 3). Most infected men attending an STD clinic were between the ages of 20 and 30.

Signs or symptoms of cervical infection in women are mucopurulent endocervical discharge

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Adapted from the author's presentation at the seminar "Sexually Transmitted Diseases" held at The Mount Sinai Medical Center on March 23, 1990. From McMaster University. Address reprint requests to the author, who is Director and Professor of Pediatrics and Pathology, McMaster University Regional Virology and Chlamydiology Laboratory, St. Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario, Canada L8N 4A6.

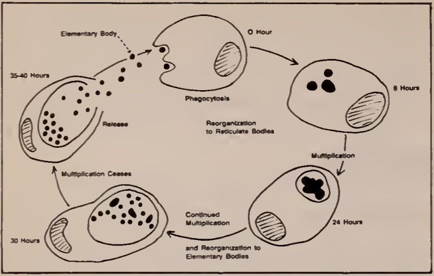

Fig. 1. Life cycle of *Chlamydia trachomatis*.

and spotting following intercourse. If ascending infection takes place and the endometrium becomes infected, intermenstrual bleeding is a characteristic sign, as is salpingitis and lower abdominal pain.

Neonatal Infections. The infant who is born to a mother with an infected cervix may develop pneumonia from three weeks to three months after birth. Conjunctivitis is a calculated risk of about 50% in the absence of prophylaxis. Neonatal chlamydial pneumonia has a 20% risk of developing in these infants. The disease is characterized by bilateral interstitial infiltrates, usually accompanied by hyperinflation. The onset of chlamydial pneumonitis is gradual and, unlike the viral pneumonias, patients are afebrile. The laboratory findings in these children are characterized by elevated IgG and IgM levels, and *Chlamydia* IgM antibody is present in high titer.

Prevention and Treatment of Infections. The current recommendations (published 1989) by the Centers for Disease Control (Table 4) include the use of erythromycin ophthalmic ointment for preventing ophthalmia neonatorum. Uncomplicated urethral, endocervical, or rectal infections should be treated with doxycycline or tetracycline. Infected pregnant patients should receive erythromycin.

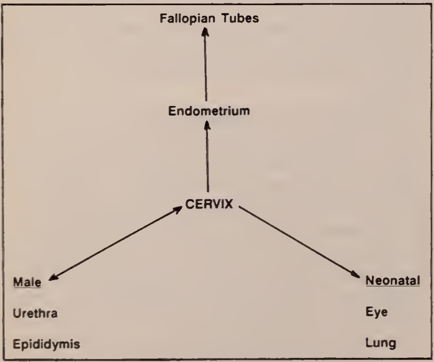

Fig. 2. Central role of uterine cervix in epidemiology of chlamydial infections.

Laboratory Diagnosis. Sampling is extremely important in diagnosis because it is absolutely essential to obtain epithelial cells that contain organisms or antigens. We have found that some swabs are better than others for collection. Cotton-tipped swabs on either a plastic or an aluminum shaft tend to give the best yield in cell culture. At the present time, the laboratory tests we have at our disposal are cell culture, direct antigen detection, DNA probes, and serum antibody.

Serologic study does not generally speaking contribute to accurate diagnosis for chlamydial infection, except perhaps in two situations: IgM testing of newborn serum to diagnose chlamydial pneumonia, and diagnosis of tubal factor infertility by testing sera for elevated IgG titers in the microimmunofluorescence test. The use of DNA probes is still experimental. Some kits are on the market, but I think that more clinical evaluations need to be performed. So what is available is cell culture and direct antigen detection. Cell culture has always been the gold standard. A diagnosis is available within 48 hours using cytochemical stains such as iodine or Giemsa, or in 24 hours using immunofluorescent monoclonal antibodies.

TABLE 1

Chlamydial Infections in Men and Women

Men	Women
Conjunctivitis	Conjunctivitis
Postgonococcal urethritis	Cervical infection
Nongonococcal urethritis	Urethral infection
Epididymitis	Endometritis
Prostatitis	Salpingitis
Reiter's syndrome	Pelvic inflammatory disease
Infertility	Perihepatitis
	Ectopic pregnancy
	Infertility

Antigen Detection. In clinical specimens the big thrust in recent years has been to use commercially available kits to search for the presence of antigens. A recent review of the literature showed 35 studies comparing antigen detection assays (Table 5). The performance ranges reported are enormous. The results reported for antigen detection with either fluorescent monoclonal antibodies or enzyme immunoassays, compared to culture, ranged from 50% to 100%. Elimination of the one or two low reports shows that both antigen detection approaches will have a sensitivity range between 70% and 100%. Specificity falls between 90% and 100%. These are very effective assays which do not require infectious organisms.

The IDEIA test measures *Chlamydia* lipopolysaccharide antigens on the organism and free in the clinical specimen, whereas the Chlamydiazyme test measures antigens that are present on the organism. A study (Table 6) performed in Hamilton, Canada, comparing the sensitivity and specificity of these two enzyme immunoassays showed differences in sensitivity both in men (62% to 81%) and in women (96% to 85%), which may be due to the population sampled, what the particular test measures, and the amount of lipopolysaccharide or outer membrane protein there is in the specimen. We took the detector reagents out of the commercial kits and performed Western blots on them to find that they measure different antigens.

Antigen Detection in Urine. In a comparison of cell culture of either urethral or cervical swabs with antigen detection using three different assays (IDEIA, Chlamydiazyme, and Microtrack) performed on urine, 224 men and 228 women were studied. There were 33 men and 12 women who had culture-positive swabs. Twenty-four of the 33 men were positive in all 3 antigen detection assays in the urine. A variable few had different combinations of positive results in urine. Considering that the true number of positives equals all the patients who are culture positive from swabbing or positive in at least two of the antigen detection assays, one can make a more accurate calculation of sensitivity (Table 7). In women, culturing the cervix was 92.3% sensitive, whereas culturing urine was only 15% sensitive. In antigen detection assays of female urine, the range was 61% to 77%. In the 38 men, culturing the urethra was 86.8% sensitive, whereas culturing the urine was 23.7% sensitive. Detection of antigens in the urine was as sensitive as culturing the urethra. All the tests calculated 100% specificity in this study group.

Some interesting new data are emerging on antigen detection in urine as well as cervical and urethral swabbing among women attending Planned Parenthood clinics in Hamilton, Canada. The number of women enrolled so far in this study is 751. A culture or Chlamydiazyme test, confirmed by blocking performed with a cervical swab, yielded a prevalence rate in this population of 751 women of about 5%. Performing a culture

TABLE 2
Clinical Characteristics of Gonococcal and Nongonococcal Urethritis

Clinical characteristic	Gonococcal urethritis	Nongonococcal urethritis
Incubation period	2–8 days	10–20 days
Onset	Abrupt	Gradual
Dysuria	Prominent (occasionally absent)	Variable (often absent)
Urethral discharge		
Purulent	74%	11%
White	22%	56%
Clear	4%	33%

TABLE 3
Age and Sex Distribution of Subjects Positive for C. trachomatis *by Cell Culture in Hamilton, Ontario, Canada (1990)*

Age (yr)	Men* No./total (%)	Women† No./total (%)
<20	5/35 (14.3)	15/27 (55.5)
20–30	28/35 (80)	10/27 (37)
30–40	2/35 (5.7)	2/27 (7.4)
>40	0/35 (0)	0/27 (0)
Total	35/35 (100)	27/27 (100)

* Attending a sexually transmitted disease clinic.

† Attending a planned parenthood clinic.

TABLE 4
Guidelines for Prevention and Treatment of Chlamydia trachomatis *Infections*

Prevention of ophthalmia neonatorum

Erythromycin (0.5%) ophthalmic ointment, once, or
Tetracycline (1%) ophthalmic ointment, once, or
Silver nitrate (1%) aqueous solution, once

Treatment of neonatal infections

Erythromycin, 40 mg/kg orally daily in 4 divided doses for at least 14 days

Treatment of uncomplicated urethral, endocervical or rectal infections

Doxycycline, 100 mg orally 2 times a day for 7 days, or
Tetracycline, 500 mg orally 4 times a day for 7 days, or
Erythromycin base, 500 mg orally 4 times a day or equivalent salt for 7 days, or
Erythromycin ethylsuccinate, 800 mg orally 4 times a day for 7 days, or
Sulfisoxazole, 500 mg orally 4 times a day for 10 days or equivalent

Treatment in pregnancy

Erythromycin base, 500 mg orally 4 times a day for 7 days, or
Erythromycin base, 250 mg orally 4 times a day for 14 days, or
Erythromycin ethylsuccinate, 800 mg orally 4 times a day for 7 days, or
Erythromycin ethylsuccinate, 400 mg orally 4 times a day for 14 days, or
Amoxicillin, 500 mg orally 3 times a day for 7 days (data are limited on this regimen)

TABLE 5

Performance of Fluorescent Antibody (FA) and Enzyme Immunoassay (EIA) Compared to Culture for the Diagnosis of Genital Infection Reported in the Peer-Reviewed Literature January 1, 1990

Assay	No. of studies	Prevalence % range	Performance % range	
			sensitivity	specificity
FA				
Cervix	25	4.4–25.3	55.9–100	82–100
Urethra	10	11–30	49–100	96–100
EIA				
Cervix	16	5.2–48.2	44.4–100	92.9–98.1
Urethra	9	20–42.6	70–92	90–100

TABLE 6

Percent Sensitivities and Specificities of IDEIA and Chlamydiazyme Compared with Cell Culture of Male Urethral and Female Cervical Swabs, Hamilton, Canada

Assay and sex	% Sensitivity	% Specificity
IDEIA		
Men	62.5 (20/32)	99.5 (199/200)
Women	96.3 (26/27)	97.9 (422/431)
Total	78.0 (46/59)	98.4 (621/631)
Chlamydiazyme		
Men	81.8 (27/33)	99.5 (199/200)
Women	85.2 (23/27)	99.3 (428/431)
Total	83.3 (50/60)	99.4 (627/631)

TABLE 7

Sensitivities of Culture and Antigen Detection Assays for Diagnosis of C. trachomatis *Infections*

Specimen, test	Sensitivity (%) Men (n = 38) No. (%)	Sensitivity (%) Women (n = 13) No. (%)
Cervical or urethral swab, culture	33 (86.8)	12 (92.3)
Urine sediment		
Culture	9 (23.7)	2 (15.4)
IDEIA	31 (81.6)	9 (69.2)
Chlamydiazyme	33 (86.8)	10 (76.9)
Microtrak	33 (86.8)	8 (61.5)

or Chlamydiazyme test on the cervical swab yielded a prevalence rate of about 5%. Performing the same two assays on just the urethral swabs yielded a rate of about 3%. Thus more than half of the infected women had an infected urethra, and all of the women who had an infected urethra were also infected in the cervix. In this population of women, therefore, no advantage is gained by taking the extra urethral swab to pick up more positives. Performing antigen detection on urine from the women detected 20 positives, which is almost the number determined by swabbing the urethra. It appears that using urine as a specimen in women is not as helpful as in men. There are so few studies of this type that more data are needed before conclusions are drawn.

Questions and Answers

Question: What is the outcome if you use wooden swabs instead of plastic or aluminum?

Chernesky: We found that the wooden swabs we used were toxic either to the cell culture or to the organism because some of them contain resins. The best rates for cotton on plastic or aluminum were 80% to 90%, whereas the rate for wooden swabs was about 40%.

Question: Have you evaluated the cytobrush?

Chernesky: We have not had much experience with cytobrushing. I've spoken with Dr. Schachter in San Francisco and he, like you, has evaluated brushes and has published his findings, which were very good.

Question: Do you have any information on the Gen-Probe DNA hybridization assay?

Chernesky: I haven't had any personal experience with that particular test. I was at a meeting recently in Canada in which two laboratories reported on the Gen-Probe assay as compared to culture and Chlamydiazyme, and the results were not very promising. The sensitivity was about 65%. I think there are not enough studies at the present time to draw any meaningful conclusions.

Question: Could you elaborate further on broadening the "gold standard"?

Chernesky: It is becoming more acceptable to not just use culture positivity as the "gold standard." However, the best culture you should use would also have at least one blind passage. If the comparison uses at least two or three other tests which measure different antigens of the organism, we consider that a patient who is positive in 2 of the 3 antigen detection assays is a true positive, missed by culture, and should be added into the denominator for calculation. Alternatively, a patient who is culture negative but is positive in an antigen detection test which has a confirmatory component should also be considered a true positive. Doing this provides a more accurate calculation and also shows how culturing performs.

Grand Rounds

Mycobacterial Infection in the AIDS Era:

Implications for Infection Control and Employee Health

SHALOM Z. HIRSCHMAN, M.D.

THE DECADE of the 1980s witnessed the spread of human immunodeficiency virus (HIV) infection and the resulting acquired immunodeficiency syndrome (AIDS). The treatment of patients with HIV infection is fraught with several hazards for the healthcare worker. As detailed by Dr. Meryl Mendelson, there is risk of parenteral spread of HIV infection to physicians and other healthcare workers through inadvertent needlesticks or other exposure to large amounts of infected body fluid, especially blood. These hazards are well known and appreciated by most physicians.

A much more insidious, and less appreciated, hazard presented by AIDS patients is the spread of mycobacterial infection, especially *Mycobacterium tuberculosis hominis,* to the healthcare worker. The deficiency of the cell-mediated immune system that is the hallmark of AIDS results in exquisite susceptibility of the patient to infection with tuberculosis (1). It can be appreciated that AIDS patients with pulmonary tuberculosis may shed large numbers of organisms (2). Indeed, the risk is such that the healthcare worker need not directly attend the tubercular patient. Tubercle bacilli can spread through the environment of the ward, if carried by air currents, and infect the susceptible healthcare worker. Indeed, such spread of mycobacteria through air currents has been amply documented by recent studies in nursing homes (3). Both Drs. Adler and Mendelson emphasize that the diagnosis of tuberculosis in the AIDS patient often is not readily apparent, since the clinical manifestations of the disease do not conform to classical descriptions (3). Therefore, tuberculosis must be considered as a possible infection in every AIDS patient with pulmonary symptoms, and appropriate infection control procedures should be instituted immediately. This approach will not only spare many healthcare workers from infection with tuberculosis, but also prevent the free spread of infection to other patients. In Haiti, where drug addiction, homosexuality, and patients with AIDS are common, the number of cases of tuberculosis has increased and the infection has become more common in younger patients (2).

Dr. Teirstein reviews the manifestations of infection with *Mycobacterium avium-intracellulare* (MAI). It is only in recent years that the full spectrum of disease caused by this organism has been elucidated. MAI is a pathogen mainly in patients with underlying pulmonary disease with distortion of the pulmonary architecture and the immunosuppressed patient, especially the patient with AIDS. MAI infection in the patient with AIDS is usually systemic; interestingly, the central nervous system seems to be spared (4). The hazard of spread of MAI infection to the healthcare worker seems to be small, but the risk is really not known. It may be that exposure of the healthcare worker to the high inocula of MAI that are produced by AIDS patients with pulmonary infection may be more dangerous. Fortunately, there have been no reports of pulmonary infection with MAI in healthcare workers exposed to AIDS patients. Yet the possibility does exist that MAI may remain as a low-grade latent infection for many years in immunocompetent healthcare workers. Indeed, it is not known whether the healthcare worker who smokes cigarettes is at greater risk of developing such pulmonary infection.

The risk presented by the AIDS patient with

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pulmonary MAI to other patients on the ward is also not known. It may be that immunocompetent patients with underlying pulmonary disease, such as emphysema, bronchiectasis, and even congestive heart failure, may be more susceptible to infection with MAI. Such infection may not become clinically apparent until several years after the exposure. It is also not known what risk the patient with MAI poses for other immunosuppressed patients in the room and on the ward. The detection of small but definite risks will require careful prospective studies in large numbers of patients and should be a national cooperative effort.

Until the advent of effective chemotherapeutic agents for the treatment of tuberculosis, this infection constituted an important hazard for the healthcare worker. With the waning incidence of tuberculosis in the general population in the United States, physicians lost their fear of tuberculous infection. The AIDS epidemic has sharpened a new awareness in the healthcare worker of the need for self-protection and for proper infection control measures.

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Pulmonary Infection with *Mycobacterium avium-intracellulare:*

Diagnosis, Clinical Patterns, Treatment

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Abstract

Most physicians fail to recognize *Mycobacterium avium-intracellulare* (MAI) as a major pathogen for pulmonary disease among patients admitted to hospitals throughout the United States. In a review of all records of positive MAI cultures during the 10 years beginning July 1, 1979, at The Mount Sinai Hospital, New York City, we have identified 244 patients who had pulmonary disease primarily or secondarily complicated by MAI. We also identified another 243 patients as false positive for MAI infection. We classed as false positives patients who had no subsequent positive culture and whose clinical picture was and remained incompatible with MAI infection.

We identified four distinct clinical patterns in the 244 patients with true positive MAI infections: (a) pulmonary nodules ("tuberculomas") indistinguishable from pulmonary neoplasms (78 patients); (b) chronic bronchitis or bronchiectasis with sputum repeatedly positive for MAI or granulomas on biopsy (58 patients, virtually all older white women); (c) cavitary lung disease and scattered pulmonary nodules mimicking *M. tuberculosis* infection (12 patients); (d) diffuse pulmonary infiltrations in immunocompromised hosts, primarily patients with AIDS (96 patients).

The diagnosis should be established either by surgical resection and culture of resected nodules, or by three repeated positive acid-fast bacillus cultures of sputum or fluid and tissue obtained by bronchoscopy, or by biopsy of other tissue which shows granulomas and one or more positive MAI cultures.

Surgical resection is the best treatment for "solitary" MAI nodules. Multiple antituberculous drug therapy is indicated for patients with chronic infection that impairs function or causes hemoptysis. The presence of MAI in the sputum or lung aspirates of patients with AIDS usually heralds the presence of a preterminal disseminated infection.

Once upon a time atypical mycobacterial infections were encountered only on the internal medicine or pulmonary boards, and were of no clinical relevance. Illness, if it happened, occurred in far-off exotic places, probably had something to do with the peculiar way other people lived, and was never seen in New York. Wrong! Disease due to atypical mycobacterial infection, particularly *Mycobacterium avium-intracellulare* (MAI), has been increasing insidiously everywhere for the past several decades.

We discuss here the work of a group of clinicians performed in concert with Beca Damsker, a superb bacteriologist with a special interest in acid-fast bacilli. The clinicians included cardiothoracic surgeons, radiologists, and pathologists as well as medical pulmonologists. This kind of clinical research hearkens back to the great period of clinical research at teaching hospitals, when clinical investigations were performed on weekends and nights. These studies promise to

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make a contribution of value to practicing physicians and patients. The data, while answering many questions, will raise many others, which in turn will require ongoing future research.

The Timpe and Runyon classification of the atypical mycobacteria have interesting and eminently forgettable names, such as rapid and slow growers, photochromogens, and scotochromogens (1). Almost all cause disease, usually afflicting the lungs. MAI is the most common of the atypical culprits. We reviewed all the records of positive MAI cultures at the Mount Sinai Medical Center, New York, for the 10-year period beginning July 1, 1979. In order to accept MAI as the cause of the clinical lung infection, we established the following criteria: (a) three positive cultures either in sputum or specimens collected by bronchoscopy, or (b) demonstration of acid-fast bacilli in tissues or tissue culture, or (c) positive cultures in sputum or bronchoscopic specimens and a positive culture from another tissue or fluid, for example blood, urine, stool, or pleural fluid. Isolation of MAI in less than three cultures, or failure to demonstrate the organism in tissues or body fluid by stain or culture, relegated the MAI culture to the false-positive group.

Using these criteria, MAI infections occurred in four distinct clinical patterns:

- Pulmonary nodules that mimic carcinoma of the lung (78 patients),
- A syndrome of chronic cough and sputum production consistent with chronic bronchitis or bronchiectasis or both (58 patients),
- Upper lobe infiltration and cavities that simulate tuberculosis (12 patients),
- Systemic infection in patients who are immunosuppressed, almost exclusively in patients with AIDS (96 patients).

Patients in the first three groups had intact immunologic systems. In all, we found a total of 244 patients who had clinical disease related to MAI infection, and 243 patients, almost an identical number, who had false positive cultures.

Clinical Patterns

Pulmonary Nodules Imitating Lung Cancer. The chest radiograph of a 72-year-old woman revealed a nodule in the left mid lung field (Fig. 1). With computerized tomography, the mass revealed associated streaks commonly seen in peripheral primary lung cancer. Prior films revealed that the nodule had been growing slowly over a period of six years. The patient had a negative tuberculin skin test. Bronchoscopic study yielded no diagnosis. Thoracotomy was performed and a granulomatous mass was removed by wedge resection. Acid-fast bacilli were seen in the specimen and subsequent cultures grew MAI. This patient became the first of a group of 20 reported by Gribetz et al. in the *American Journal of Medicine* in 1982 (2). Since that time, we have accumulated 78 cases of such nodules. It is now quite clear that almost all "tuberculomas" are due to MAI and not *M. tuberculosis.*

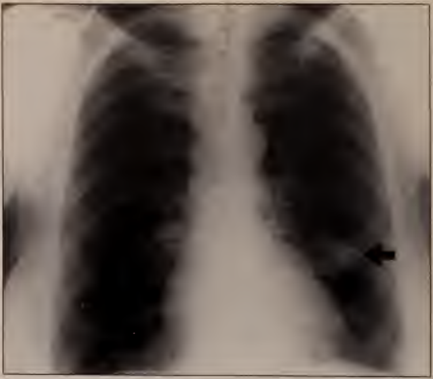

Fig. 1. Chest radiograph of 70-year-old woman revealing left mid-lung-field nodule which had been slowly enlarging for six years. Thoracotomy yielded granulomatous nodule containing acid-fast bacilli. MAI grew on culture.

Most patients with granulomas simulating carcinoma of the lung are asymptomatic, and only a few have positive tuberculin tests. Radiologically, the granulomas all mimic primary lung cancer. They grow slowly over several years. There is no way, clinically or radiographically, to differentiate these slowly growing benign granulomas from lung cancer. In some patients, specimens obtained at bronchoscopy yielded positive cultures 4 to 8 weeks after the procedure. In almost every instance the lesion was resected before the physician received the positive culture report. Even when the report of MAI was received prior to resection—a rare occurrence—surgery was indicated, since a single culture obtained at bronchoscopy was not deemed diagnostic. Furthermore, it was impossible to leave a growing peripheral nodule which might be a carcinoma. Finally, resection is the preferred treatment for MAI tuberculomas.

Acid-fast bacilli are usually, but not always, easily seen in the tissue specimens. Since we have learned that most of these granulomas are due to MAI, we now await culture reports prior to instituting antituberculous therapy. If, as expected, MAI is grown, no antituberculous treatment is prescribed. On the other hand, in the rare instance when *M. tuberculosis* grows in culture, antituberculous therapy should be instituted.

Chronic Cough and Sputum Production (Bronchitis/Bronchiectasis). The second of the clinical patterns we identified consists of patients who come to the physician coughing and spitting, occasionally with blood-streaked sputum, and with nodular and ill-defined opacities on chest radiographs. Remarkably, the overwhelming majority of these patients are women between the ages of 55 and 85.

The chest radiograph of one of the patients in our series who typically had cough and sputum production revealed middle lobe infiltrations and scarring (Fig. 2). A bronchogram demonstrated tubular changes of bronchiectasis involving the right middle lobe. This patient was producing approximately 60 cc of blood per day. Bronchoscopic specimens revealed acid-fast bacilli on smear. She had a positive PPD 5 TU skin test, and treatment with antituberculous drugs was begun. However, she did not improve. Because of continuous brisk hemoptysis she came to surgical resection. Cultures from bronchoscopic studies and the surgically removed right middle lobe grew MAI. Microscopy of the right middle lobe revealed chronic bronchiectasis and noncaseating granulomas with acid-fast bacilli. Severe hemoptysis is the prime indication for thoracotomy in this group of patients with chronic bronchiectasis due to MAI.

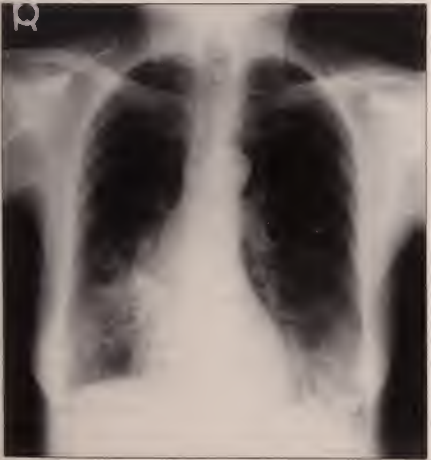

Fig. 2. PA chest radiograph of 79-year-old woman revealing middle lobe, lingula, and left lower lobe infiltrations. Repeated large hemoptysis was controlled by right middle lobectomy.

Occasionally hemoptysis is life-threatening. One example: a 52-year-old woman who had her first bout of hemoptysis when she was 46 years old. She had never been ill or had previous pulmonary symptoms. She suddenly coughed up approximately one cup of blood. Bronchoscopy was performed at her local hospital and was nondiagnostic. However, as so often happens, subsequent cultures of material obtained at bronchoscopy grew MAI, which was never reported to the patient's physicians.

She was treated for the first time at The Mount Sinai Hospital in 1981, when new shadows were seen in the right middle lobe and superior segment of the right lower lobe, coincident with another bout of massive hemoptysis. CT scanning and bronchography confirmed pulmonary nodules and bronchiectasis. Antituberculous therapy with isoniazid and rifampin was instituted. However, she developed fever and elevated ALT and AST blood tests, and treatment was discontinued.

Before another antituberculous regimen could be instituted, she suffered her third bout of massive hemoptysis, and emergency thoracotomy was performed. Resection of the right middle lobe and superior segment of the right lower lobe was performed. The specimen revealed multiple bronchiectatic areas with scattered granulomas throughout the tissue. Cultures subsequently grew MAI.

Several months later, cough productive of blood-streaked sputum reoccurred and again MAI was cultured. Therapy with rifampin, ethambutol, ethionamide, and cycloserine was begun. However, she suffered another bout of hemoptysis, requiring a second thoracotomy for control of bleeding. The bleeding was noted to come from the stump of the resected superior segment of the right lower lobe and revealed MAI granulomas on pathologic analysis.

Unfortunately, 5 years later she began to experience hemoptysis and her sputum revealed MAI. At this point treatment with the four antituberculous drugs was reinstituted. Although she developed neurologic symptoms from cycloserine treatment and severe gastrointestinal complaints with marginal elevated liver chemistry levels, the medications were continued. Fortunately hemoptysis ceased and her chest x-rays have shown clearing of residual infiltrations. She is currently working full-time as a librarian. On occasion, however, she still produces sputum from which MAI is cultured.

Questions Raised by the Bronchiectatic Syndrome. Surprisingly, most patients with bronchiectasis and bronchitis are older white women. Prince et al. reported a similar group of patients with MAI infection with the same demographic distribution (3). There is no explanation for this unique propensity for MAI bronchitis or bronchiectasis in older white women.

These patients evoke several questions. First, since most give a long history of cough and sputum production, the possibility arises that the MAI organism is a saprophyte growing in previously diseases airways or areas of suppurative bronchiectasis. MAI is a ubiquitous organism found throughout the environment in every area of the United States. It is equally possible that the MAI is the primary pulmonary pathogen.

We have reason to think that in many of our patients MAI is a pathogen rather than a saprophyte. In the entire group of 58 patients with this syndrome, 6 patients had no biopsy procedure performed; 52 had flexible bronchoscopic study with biopsy, and 7 of these patients came to surgical resection because of recurrent hemoptysis. Nineteen of the bronchoscopic biopsies and all 7 of the surgical specimens revealed granulomatous infection with MAI. In the remaining 32 (of 58) patients, MAI was recovered by culture of the bronchoscopic specimens, but no granulomas were noted by bronchoscopic biopsy.

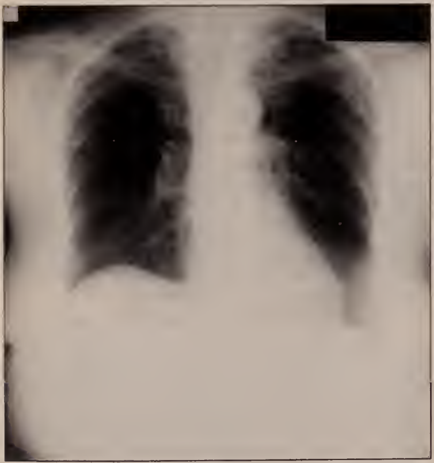

Fig. 3. PA chest radiograph of 69-year-old woman revealing bilateral upper lobe infiltrations mimicking tuberculosis. Bronchoscopic biopsy revealed noncaseating epithelioid granulomas. Cultures grew MAI.

In the 26 patients with pathologic proven MAI granulomas, it is reasonable to assume that the MAI was a pathogen. However, we cannot be certain about the other 32. Although they repeatedly had positive cultures for MAI, we were unable to demonstrate granulomas in the tissue, despite finding 3 or more positive cultures for MAI.

Nevertheless, it would appear that in an elderly woman who is coughing and producing MAI in the sputum, with an abnormal chest radiograph suggesting the diagnosis of bronchiectasis, it is prudent to assume that MAI is a true pathogen, either primary or secondary.

MAI Infection Simulating *M. tuberculosis*. On the chest radiograph of a 69-year-old woman (Fig. 3), one of the patients in our series, bilateral upper lobe infiltrations indistinguishable from classic *M. tuberculosis* infection were demonstrated. This patient's tuberculin skin test was negative. At bronchoscopy, the biopsy revealed granulomas from which acid-fast bacilli were cultured. We assumed that she was one of the rare patients with active tuberculosis despite a negative skin test. We were surprised when only four weeks later, MAI and not *M. tuberculosis* grew in culture. Tuberculin skin testing is an important diagnostic test in differentiating these two mycobacteria. Although the vast majority of patients with *M. tuberculosis* infection will exhibit a positive tuberculin skin test, less than 30% of our group of immunocompetent patients with MAI infection had a positive tuberculin test.

The preferred radiographic locations for *M. tuberculosis,* and to a lesser extent for MAI, are the apical and posterior segments of the upper lobes and the superior segment of the lower lobes. MAI infection may occasionally involve the anterior segment of the upper lobe (Fig. 4). Cavities occur with equal frequency in *M. tuberculosis* and MAI disease.

Thus, the radiographic and clinical picture of MAI pulmonary infection can be a duplicate of the radiographic and clinical picture of *M. tuberculosis*. One of our patients had been successfully treated for culture-proven *M. tuberculosis* infection 25 years prior to consulting our service. His cavity remained bacteriologically negative and "open healed." In 1987 he had his first episode of hemoptysis. He repeatedly produced sputum that grew MAI rather than *M. tuberculosis*. Because of persistent hemoptysis, he underwent resection of the right upper lobe cavity. The pathologic specimen revealed caseous necrosis with acid-fast bacilli, but the cultures grew only MAI.

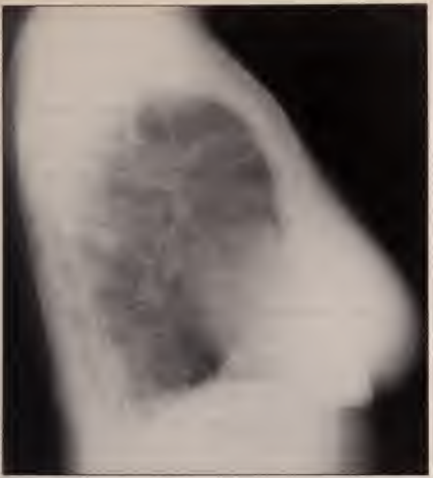

Fig. 4. Right lateral chest radiograph of 64-year-old woman revealing cavitary lesion under sternum in anterior segment of right upper lobe. Cultures of bronchoscopic specimens revealed MAI. Radiographic shadows cleared with four-drug antituberculosis therapy.

Immunosuppressed Patients. Immunosuppressed patients with MAI infection were almost exclusively afflicted with AIDS. The role of MAI as a primary lung infection in these patients is problematic. They usually have opportunistic infections and are quite short of breath, with persistent cough and sputum production. Results of chest radiographs range from normal to areas of local consolidation, nodulation, pulmonary cysts and bilateral diffuse infiltrations. Many of these abnormal parenchymal patterns are accompanied by mediastinal and hilar lymph node enlargement. Most of these radiographic abnormalities in patients with AIDS are due to *Pneumocystis carinii, M. tuberculosis,* various bacterial infections, cytomegalovirus, fungi, nonspecific pneumonitis, or lymphocytic interstitial pneumona.

In many patients, repeated smears and cultures of pulmonary specimens were found to grow MAI. However, in every one of our patients with AIDS and positive cultures for MAI, the MAI was also found in biopsy tissue, blood, stool, pleural fluid, pericardial fluid, or urine, indicating the presence of a disseminated infection involving multiple organs and sites. At autopsy almost every organ, most commonly liver, spleen, and lymph nodes, yielded positive cultures for MAI. Interestingly, because of the T-cell defect in AIDS, many of these patients were unable to form typical granulomas and did not exhibit the classic pathology of an acid-fast bacillus infection.

It is apparent that in these patients, the pulmonary presentation is part of a systemic MAI infection with an attendant extremely poor prognosis and is not a primary pulmonary infection, whereas in the three nonimmunosuppressed groups of patients we studied—patients with nodules, patients with bronchitis-bronchiectasis, and patients with upper lobe or superior segment infections mimicking tuberculosis, the infection is a primary pulmonary condition. The ultimate prognosis in the latter three groups is excellent. We encountered no deaths due to MAI in these patients. On the other hand, the outcome of AIDS patients with disseminated MAI involving multiple organs and fluids is almost universally fatal.

Treatment

Patients with Nodules Simulating Lung Cancer. When a patient has a chest radiograph exhibiting a growing nodule, surgical resection is indicated. This nodule is not a medical disease. After the surgical resection, when you have learned that the nodule was a granuloma due to MAI and not a carcinoma, buy your patient a bottle of champagne and celebrate. The patient did not have cancer and you have administered the best treatment for the MAI nodule. We have seen no second MAI nodules and no spread of MAI disease in these patients who underwent resection. None of the last 50 patients with MAI nodules were given postoperative antituberculous therapy.

Patients with Chronic Bronchitis and Bronchiectasis. The older patients who have the bronchiectatic syndrome are much more difficult to treat. Most of them will have some untoward reaction to one or more antituberculous drugs. The frequency of abnormal levels in liver chemistry studies with the picture of chemical hepatitis is increased in older patients. Before a coughing and spitting 70-year-old woman whose chest radiograph reveals shadows is treated with three to five antituberculous drugs, the physician must ask whether the treatment will be worse than the illness. However, some of these patients can become quite ill with impaired pulmonary function and hemoptysis and will require multidrug therapy. In Prince's group (3), 5 similar patients died because of progressive MAI infection. The group we have studied has not experienced any mortality, although several patients have come to surgery because of repeated life-threatening pulmonary hemorrhage.

Some of these patients who chronically cough and produce sputum are also infected with common bacteria. Judicious use of conventional antibiotics may be quite helpful in controlling the cough and sputum production without antituberculous medications.

When the patient's symptoms are intolerable, when hemoptysis is major, or when pulmonary function is threatened, multiple-drug antituberculous therapy is indicated. In these older patients with a high frequency of drug reactions, antituberculous therapy for MAI should start with a single drug, not with isoniazid and rifampin together, in order to pinpoint adverse drug reactions. Pyridoxine, 50 mg/day, should be added, since neuropathy is more common in older patients. Surprisingly, a few patients may improve clinically and radiographically on therapy consisting only of two antituberculous drugs. Unfortunately, some will not respond even to as many as five medications, and you may finally throw up your hands and say, "I am sorry, Mrs. Smith, you will have to cough and spit, because these medicines are not working and are too toxic."

Patients with Infiltrations and Cavities Simulating Tuberculosis. Patients with the tuberculosislike syndrome are treated exactly the same as are those with bronchiectasis: as few antituberculous drugs as possible. If hemoptysis is prominent, surgical resection may be required. Since patients with cavitary lesions usually have localized disease, surgery almost always will provide a clinical cure.

Patients with MAI Infection and AIDS. The outcome for those patients who have AIDS and MAI infection is almost universally dismal. The usual prescription is for as many antituberculous drugs as the patient can tolerate, including some of the newer medications, such as ansamycin, clofazamine, and quinolone antibiotics. However, these patients usually have disseminated MAI infection in which not only the lungs but many organs are involved. Demonstration of MAI in lymph nodes and other organs as well as in the lungs is usually evidence that the patient has a disseminated terminal disease.

Summary

MAI infection occurs as a pathogen in four distinct clinical presentations. A large number of affected patients will have nodules that appear to be carcinoma. These should be surgically removed.

The second common group of patients with MAI infection will be elderly women with chronic cough and copious sputum production and a clinical picture consistent with chronic bronchiectasis. Treatment depends on the severity of the illness. If the cough and sputum production or pulmonary dysfunction are severe, a trial of multiple antituberculous drugs is indicated. Unfortunately, many patients will not tolerate the requisite drug regimen. A subset of these patients will have significant hemoptysis, which may require surgery to control life-threatening hemorrhage.

A third small group of patients will exactly resemble patients with *M. tuberculosis* infections. They also will require drug treatment or surgical resection. Finally, the fourth group of patients, all immunocompromised and almost all with AIDS, have MAI infection usually as the final opportunistic assault of their disease. Therapy consists of multiple antituberculous drugs but almost never has a positive impact on the outcome of their disease.

Importantly, before accepting a diagnosis of pulmonary disease due to MAI, you must be certain that MAI is the pathogen. This can be accomplished only be setting strict bacteriologic criteria. We have encountered an almost identical number of false positive cultures for MAI as we have true positive identifications of MAI as the pathogenic organism. Thus, the diagnosis of pathogenic MAI disease must be buttressed by three positive cultures and/or demonstration of MAI in biopsy specimens or body fluids that are usually sterile.

Questions and Answers

Richard Gorlin: Thank you very much, Dr. Teirstein. You have emphasized the distinction between *M. tuberculosis* and *M. avium-intracellulare.* Obviously, they are different organisms, but in the non-AIDS patients, is there anything different about the natural history of one mycobacterium when compared to another? They seem so much alike clinically, if not in prevalence. Does it make a difference whether you find *M. tuberculosis* or MAI? Isn't treatment going to be the same?

Teirstein: AIDS patients with *M. tuberculosis* infection respond surprisingly well to antituberculous treatment, and recovery from tuberculosis in the immunosuppressed group is common. MAI infection in AIDS carries a much worse prognosis; death can be anticipated. For those immunocompetent patients who comprise the other three groups subject to MAI infection, it makes a great deal of difference whether the infection is due to MAI or *M. tuberculosis*. MAI is not contagious and no infection-control precautions are necessary. Resection of a lesion in patients with *M. tuberculosis* should be followed by antituberculosis therapy, whereas MAI granulomas require no follow-up therapy. Finally, if patients with MAI disease require antituberculous treatment, they will need multiple antituberculous drugs and are more likely to have a drug reaction than patients with *M. tuberculosis*. I daresay one of the "favorite" diseases of pulmonary physicians is infection due to *M. tuberculosis;* these patients almost always recover with proper treatment. They love their doctors. Chronic infection due to MAI usually requires multiple-drug antituberculous treatment for an unspecified duration. Many of these older patients will become ill due to drug reactions. MAI infection is much more difficult to treat than *M. tuberculosis*.

Question: Is disseminated disease to the brain seen in MAI? Are urine cultures positive?

Teirstein: None of our patients with intact immune systems had disseminated disease. Not all had urine cultures for acid-fast bacilli. When cultures were performed, none had MAI recovered. In the AIDS group, several patients' spinal fluid yielded positive MAI cultures, and urine commonly had positive cultures for MAI. At postmortem examination, MAI was grown from multiple sites, including the kidneys.

Leonard Stone: How can you be sure that a culture obtained from sputum or tissue which grows MAI is a false positive?

Teirstein: We have followed up most of those patients from whom a single culture was reported to show MAI. In the vast majority, the presence of MAI was incompatible with the clinical picture. In all, no subsequent cultures were positive, no antituberculous therapy was administered, and MAI infection played no part in their subsequent clinical picture.

Gorlin: Thank you very much for a very illuminating discussion.

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Grand Rounds

HIV Infection in Healthcare Workers: Risk and Prevention

Meryl H. Mendelson, M.D.

The risk of transmission of the human immunodeficiency virus (HIV) in the healthcare environment has been best estimated by several large prospective studies that have followed healthcare workers who have sustained injuries or exposures to the blood of HIV-infected patients.

Risk of Transmission

The rate of infection (assessed by seroconversion from HIV-antibody negative to positive) after accidental needlestick injury involving HIV-positive blood based on cumulative data from three large studies of healthcare workers at San Francisco General Hospital, the National Institutes of Health, and the Centers for Disease Control (CDC) has been estimated to be approximately 0.4% or 1 infection in every 250 needlestick injuries (1–4). In an updated summary by the CDC, as of December, 1988 there were 1,107 healthcare workers enrolled in the CDC study who had sustained parenteral, mucous membrane, or nonintact-skin exposures to HIV-positive blood. Of the 982 healthcare workers with needlesticks or cuts with sharp objects, 4 tested positive (2). However, no baseline specimen was available for one of these workers, so that it was not possible to confirm that the needlestick was the cause of the infection.

When mucous membrane exposures or exposures to broken skin have been evaluated prospectively, no seroconversions have been reported. An estimation of risk for HIV seroconversion following mucous membrane exposure using a 95% confidence interval has been calculated to be 0.32% (2). The Centers for Disease Control has reported that three healthcare workers who sustained a mucous membrane or broken skin exposure subsequently converted to HIV antibody-positive (5). These reports remain separate from the prospective study.

Additional practical questions on the risk of transmission in the healthcare setting persist. Of concern is the risk of HIV transmission following a needlestick from an unknown source. To assess risk, it is necessary to know or estimate the prevalence of HIV infection in the population from which blood has contaminated the implicated needle. This data, however, is scarce, and is not in general available for hospitals and healthcare facilities across the country. The CDC has published a chart that delineates the calculation of risk of HIV infection from a needlestick from an unknown source (6). If, for example, the prevalence of HIV positivity is 5%, and if the risk of seroconversion is estimated to be 0.4% (after a known HIV-positive exposure), the risk of seroconversion when a needlestick occurs from such a population would be approximately 0.02%. This information is useful to healthcare workers when they sustain such an injury or are concerned as to the general risk for their particular occupation.

Preventing Transmission: Universal Precautions

Although the risk for acquisition of HIV infection in the healthcare setting has been shown to be extremely small after any individual exposure, efforts must be made to prevent exposures, because that is the only sure mode of preventing transmission. The CDC prospective study notes that two injuries that resulted in seroconversion were from a co-worker during a resuscitation procedure, suggesting that those injuries may

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have been preventable (2). Further prospective data from Canada have indicated that of 234 healthcare workers with various types of exposures, approximately 40% probably could have been prevented (7). In an effort to prevent exposures, healthcare facilities have adopted universal precautions delineated by the CDC and accepted by the Occupational Safety and Health Administration (see box).

The major element in the Universal Precautions is the assumption that every patient is HIV-positive or carries in their blood a potentially transmissable agent—hepatitis B virus, human immunodeficiency virus, virus(es) causing non-A non-B hepatitis. Screening all patients in advance is not practical and in addition may give a falsely lower number than the number of actual carriers of HIV, because during the latency period prior to seroconversion, persons have been shown to carry HIV but test negative for HIV antibody (8).

A second major element in the precautions is that the measures be routinely used in order to prevent skin and mucous membrane exposures when contacting blood or body fluids.

Particular precautions must always be taken when handling sharp instruments of any sort.

Blood and Body Fluids Implicated in HIV Transmissions. Blood is the single most important potential source of tramsmission of HIV and other blood-borne infectious agents in the healthcare setting. Other body fluids included in the Universal Precautions because they have been implicated in HIV transmission in other settings or because the HIV virus has been isolated from them are semen; vaginal secretions; cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids. In addition, any other body fluid that contains visible blood should also be handled in accord with the precautions (1).

Management of Exposure to Blood and Body Fluids in the Healthcare Setting

Occupational exposures are categorized by type: percutaneous, contact with mucous membranes, and contact with skin. Percutaneous exposures are those that are secondary to a needlestick or a cut with a sharp object; mucous membrane exposures are those secondary to splatters into eyes, nose, or mouth; skin contact exposures are especially likely when skin is chapped, abraded, or dermatitic, or when the contact is prolonged or involves an extensive area of skin.

Universal Precautions When Treating Any Patient To Prevent Transmission of Blood-Borne Infectious Diseases

Appropriate barrier precautions should be routinely used to prevent skin and mucous membrane exposure when contact with blood or body fluids of any patient is anticipated.

Wear gloves when touching blood, body fluids, mucous membranes, nonintact skin; handling items or surfaces soiled with blood or body fluids; performing venipuncture and other vascular access procedures. Gloves should be changed after contact with each patient.

Wear masks and protective eyewear or face shields during procedures likely to generate droplets of blood or body fluids to prevent exposure of mucous membranes of mouth, nose, and eyes.

Wear gowns or aprons during procedures likely to generate splashes of blood or body fluids.

Wash hands and other skin surfaces immediately and thoroughly if contaminated with blood or body fluids. Wash hands immediately after gloves are removed.

Precautions should be taken to prevent injuries caused by needles, scalpels, and other sharp instruments or devices (during procedures, cleaning, disposal).

Needles should not be recapped, purposely bent or broken by hand, removed from disposable syringes, or otherwise manipulated by hand.

After use, disposable syringes and needles and other sharp items should be placed in puncture-resistant containers.

Healthcare workers with exudative lesions or weeping dermatitis should refrain from all patient care and from handling patient-care equipment until the condition resolves.

Adapted from Centers for Disease Control, Recommendations for Prevention of HIV Transmission in Health-Care Settings, MMWR 1987; 36 (Suppl. no. 2S):3S–18S.

An exposure is defined to occur after contact has been made with blood, tissue, other body fluids as defined above, or any body fluid contam-

Universal Precautions—Invasive Procedures

Invasive Procedure: surgical entry into tissues, cavities, or organs, or repair of major traumatic injuries.

Operating room, delivery room, emergency room, or outpatient physician's or dentist's office.

Cardiac catheterization and other angiographic procedures.

Manipulation, cutting, or removal of any oral or perioral tissues including tooth structure.

Attire

Gloves

Surgical masks

Protective eyewear or face-shields

Gowns or aprons

If a glove is torn or needlestick or other injury occurs, glove should be removed and a new glove used as promptly as safety permits; the needle or instrument involved in the incident should also be removed from the sterile field.

Adapted from Centers for Disease Control, Recommendations for Prevention of HIV Transmission in Health-Care Settings, MMWR 1987; 36(Supp. no. 2S):3S–18S.

Management of Persons After Occupational Exposure

- Report immediately to Employee Health Service or Emergency Room
- Evaluation and determination of exposure
- Evaluation of source
  Hepatitis status (B, non-A non-B)
  HIV status and risk
- Evaluation of hepatitis status of exposed worker
- Administration of hepatitis prophylaxis
- Source testing for HIV after consent
- Offer administration of zidovudine for prophylaxis
- Counseling of exposed worker on PHS recommendations for preventing transmission of HIV:
  - refraining from blood, semen, organ donation
  - abstaining from, or using measures to prevent transmission during, sexual intercourse
  - no breast feeding

inated with blood, and in addition, with laboratory specimens that contain the HIV virus—for example, suspensions of a concentrated virus (1).

Management Protocol. Following an exposure as defined above, healthcare workers are advised to report immediately to their employee health service or emergency room if the exposure occurs in a hospital or to their physician or local emergency room if the exposure occurs outside a hospital.

The management protocol (see box) should begin with the evaluating physician or practitioner determining whether an exposure has occurred and what the extent of exposure is. Although no definite data exist on the relationship between likelihood of transmission of HIV and extent of exposure, and although exposure has been reported after superficial needlesticks, it is suspected that deeper parenteral exposures as well as injections of blood or parenteral exposures from laboratory specimens with high titers of virus would pose a higher risk (9).

Information on the source of the blood or body fluid must be obtained at the time of evaluation. This includes hepatitis B status (HBsAg), HIV status (AIDS, ARC, HIV seropositivity, or member of risk group), and history of non-A non-B hepatitis (liver disease, abnormal liver function tests, history of multiple transfusions, and so on).

Hepatitis. Prophylaxis for exposure to hepatitis B depends on the status of the source and the prior immunization history of the exposed worker (10). For optimal efficacy, administration of hepatitis B immune globulin (HBIG) should take place as soon as possible; efficacy beyond 7 days is unclear. When the source of the blood is HBsAg-positive, HBIG should be given preferably within 24 hours. Hepatitis B vaccine is administered within 7 days, and the vaccine series is continued. More detail on postexposure prophylaxis is available in the CDC's 1990 recommendations, "Protection against Viral Hepatitis—Recommendations of the Immunization Practices Advisory Committee (ACIP)" (10). Postexposure prophylaxis for hepatitis B has been shown to be at least 75% efficacious (10). Although prophylaxis for non-A non-B hepatitis does not have the proven efficacy of that for hepatitis B, the CDC recommends offering immunoglobulin (0.06 mL/kg) following such exposures.

HIV. A detailed assessment of the HIV risk of the source needs to be made. If the source is noted to be at risk and does not have a known HIV-related illness or known seropositivity, the source should be approached for consent to testing for HIV antibody. Sources who are not known to be at risk may also be approached and tested.

HIV testing of the exposed worker is indicated as well. This is recommended at the time of exposure, and at 6 weeks, 12 weeks, 6 months, and 1 year following exposure.

The worker needs to be counseled not only on the risk of seroconversion following exposure, but also on the Public Health Service recommendations regarding prevention of transmission of HIV to others. These recommendations include refraining from blood, semen, and organ donation; abstaining from or using measures to prevent transmission during sexual intercourse (latex condoms); discontinuing breast feeding (1). The recommended period of time for following these measures is at least 6 months, the period in which most persons who have acquired HIV infection from healthcare-related exposures have seroconverted. If prophylaxis is administred (zidovudine), this period of time has not been determined.

In addition, the healthcare worker is counseled on recognition of the acute illness ("acute AIDS retrovirus infection or primary HIV infection") that has been reported to occur prior to seroconversion (11). This illness is an acute infectious mononucleosis-like illness with nonspecific clinical symptoms and signs, including fever, malaise, anorexia, nausea, myalgia, arthralgia, headache, sore throat, diarrhea, and generalized lymphadenopathy. In addition, a macular erythematous eruption has been reported.

Chemoprophylaxis with AZT. Attempts have been made to evaluate chemoprophylaxis with zidovudine following exposure to HIV in both animal and human studies. The Public Health Service Statement on Management of Occupational Exposure to Human Immunodeficiency Virus (1/26/90) (1) includes the following assessments:

- "Data from animal studies are inadequate to support or reject the hypothesis that zidovudine may be effective prophylaxis for persons who have been occupationally exposed to HIV."
- "The efficacy of zidovudine prophylaxis for humans after exposure to HIV cannot be assessed because of insufficient data."

The animal studies have reported variable efficacy of prophylactic zidovudine. Initial studies in mice injected with a large challenge of Rauscher murine leukemia virus (RMLV) demonstrated a lack of viremia in animals given a 20-day course of zidovudine beginning 4 hours after inoculation (12). A 6-week course of zidovudine (beginning one hour postinoculation) given to cats injected with Rickard feline leukemia virus (RFLV) prevented infection in 7 of 8 cats. A less protective effect was noted when zidovudine was initiated 3 to 7 days following inoculation (13).

Studies in primates have been less promising. Two of three macaque monkeys treated with zidovudine within 1 hour of inoculation with simian immunodeficiency virus developed infection (14). In addition, in an immunodeficient mouse model (reconstituted with human hematolymphoid organs), zidovudine administered 24 hours prior to injection did not prevent HIV infection following intrathymic injection of HIV (15).

Studies in humans have essentially been limited to one double-blind placebo-controlled study sponsored by Burroughs Wellcome in which a 6-week course of zidovudine (200 mg every four hours) was administered to 49 healthcare workers (45 received placebo) who had experienced percutaneous, mucous membrane, or nonintact skin exposures to HIV-infected blood. None developed HIV infection after six months (1). Individual reports of zidovudine prophylaxis have included failure of a 6-week course initiated 7 days following a blood transfusion from an HIV-infected donor (1) and failure following zidovudine administered within 45 minutes of an accidental intravenous injection of 100–200 μl of HIV-positive blood (16).

In two research laboratory workers treated with zidovudine within 24 hours following exposure of abraded or broken skin to high concentrations of HIV, the result was seronegativity at 3 months of one exposed worker and seronegativity of the other exposed worker at 11 months (1).

Despite these two reports of success, it is clear that the Public Health Service statement characterizing the data on the efficacy of zidovudine as postexposure chemoprophylaxis must be stressed to all exposed persons being counseled. Thus the decision to take zidovudine in such circumstances rests with the exposed employee (9).

Toxicity of AZT in Healthy Persons. Data on the toxicity of zidovudine when given to healthy persons not infected with HIV is limited. In the Burroughs Wellcome study (1), reports of side effects included nausea and vomiting (the most frequent complaints); 28.6% had a hemoglobin level of 9.5–12 g/dL, compared to 2.9% with such hemoglobin levels in the placebo group. The percentage of AZT takers who elected to discontinue the drug because of subjective reversible symptoms, including nausea, vomiting, fatigue, headache, myalgia, or cough was 14.3%, whereas among placebo takers only 2.9% elected to discontinue.

The long-term effect of zidovudine on mutagenicity is unknown. Studies in mice have reported vaginal tumors (including carcinomas) in animals receiving zidovudine at doses that achieved plasma levels equal to therapeutic human plasma levels. In rats, however, tumors were not induced until levels of the drug in plasma reached 10 times therapeutic human plasma levels. Of note, however, was the development of tumor following at least 19 months of treatment (17). The applicability of this data to humans, and in shorter courses of treatment, is not clear. Such complications are expected to be rare because, although zidovudine is active at the level of DNA polymerase enzymes, human enzymes do not easily use AZT triphosphate as a substrate (9).

The effect on the fetus and on reproductive capacity and whether AZT is excreted in milk is not known (1).

Zidovudine is offered to individuals who have sustained an exposure to HIV-infected or potentially HIV infected blood or body fluids (as defined above). If the individual decides to begin or is undecided, it is urged that they begin as soon as possible or at least begin with an initial dose and then continue the consideration process. The individual signs a consent form that explains the discussion of the efficacy of AZT and of its potential adverse effects. Laboratory studies (complete blood count and so on) are repeated during the 6-week treatment period. Dosages employed have been 200 mg every 4 hours (9).

Summary

Patients with HIV infection pose a minimal but real risk to healthcare providers who sustain an exposure to such patients' blood or body fluids. Using data from large prospective studies, the estimated risk following parenteral exposure to HIV-positive blood is 0.4%. When a healthcare worker sustains an exposure, Mount Sinai Infection Control recommends immediate referral of the worker to an employee health service or emergency room for evaluation of the incident. Appropriate prophylaxis for hepatitis should be administered in a timely fashion. Counseling should be provided to exposed healthcare workers on the risk for HIV infection and precautions to take in the followup period. Zidovudine should be offered in a timely fashion as well; however, the ultimate decision on that treatment rests with the person exposed.

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Resurgence of Tuberculosis:

Relationship to HIV Infection and Implications for Infection Control

MERYL H. MENDELSON, M.D., AND JACK ADLER, M.D.

TUBERCULOSIS (TB) remains an infection of worldwide importance. Best estimates are that six to eight million new cases of TB occur each year, and that two million people die annually as a result of this disease (1).

In the United States, approximately 23,000 new cases occur each year, a case rate of 9.3 cases per 100,000 population (1). Approximately 80% are pulmonary tuberculosis cases and 20% are extrapulmonary, most often lymphatic and pleural TB.

In the United States, large areas of the country have a diminishing, even a nonexistent tuberculosis problem. One state, Wyoming, did not report a single case of TB during the entire year of 1989. On the other hand, New York and other urban areas have noted an increase in TB cases over the past four to five years.

Tuberculosis in New York City

In New York City, reports of infectious disease cases must by law be submitted to the New York City Department of Health. Information on all individuals either suspected of having or proven to have tuberculosis disease is sent to the City Bureau of Tuberculosis. The criteria used to confirm a case of tuberculosis in New York City are based on the Centers for Disease Control definition; 90%–95% of cases are confirmed by positive culture of *M. tuberculosis,* and the others, especially those in children (where bacteriologic confirmation is often lacking), are confirmed by clinical criteria.

Looking closer at New York City (Fig. 1), the case load has increased from approximately 1,600 cases a year in 1984 to over 2,500 cases in 1989; the corresponding increase in rates is from 23 per 100,000 to 33 per 100,000, 3½ times the national rate (2). The 2,500 cases in New York City in 1989 represented more than 10% of the total U.S. morbidity. At the Mount Sinai Medical Center, the number of cases increased in 1989 to over 100, representing 4% of New York City's total.

Rates of Disease by Subpopulation: Age, Sex, Ethnicity. The epidemiologic study of tuberculosis in New York City pinpoints certain subpopulations that have extremely high rates of disease. For example, the highest rates are in younger people, ages 25 to 44 (Fig. 2) (2). This represents the oldest pattern of tuberculosis, similar to that in previous centuries, when TB was a virulent killer of young adults. In contrast, in other parts of the country TB has become predominantly a disease of the elderly, reservoirs of infection being described in nursing home populations.

The age distribution of disease varies not only geographically but also by racial and ethnic groups (Fig. 3). In the white population the age distribution curve is essentially flat (2). In the Asian population, the highest rates are in the elderly, probably representing the typical TB of old age resulting from the reactivation of prior infection. However, in the Hispanic and black popula-

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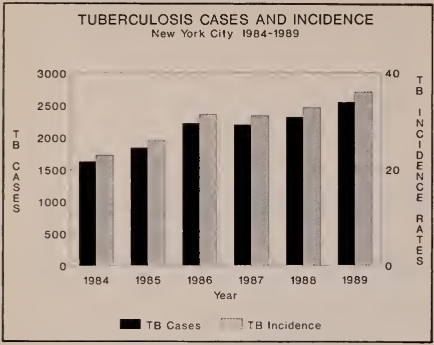

Fig. 1. New York City Department of Health data (ref. 2).

tions of New York City, the highest rates are in young adults.

When one examines the tuberculosis rates for black males (Fig. 4), over the past six years an extremely high rate of disease is noted in the group aged 25–44 years; in 1989 the rate was 400 per 100,000, 12 times the New York City rate and 44 times greater than the national rate. This astronomically high rate is greater than that in many Third World countries. A similar age distribution of TB is seen in the Hispanic male population, but the peak rate is lower, 150 per 100,000 (2).

Inadvertent Exposure. The impact of this epidemic with its specific epidemiology has been seen in many hospitals and healthcare facilities throughout the country; at The Mount Sinai Hospital in New York, for example, reported cases of tuberculosis have risen 177% from 1985 to 1989. This rise brings with it an increase in the number of persons inadvertently exposed to tuberculosis (defined as exposure to person with active pulmonary tuberculosis). In 1989, 500 employees and patients at Mount Sinai Hospital were inadvertently exposed, a characteristic figure for an urban hospital which only begins to suggest the dimensions of the problem citywide and countrywide.

The preventability of such exposure depends on the early and easy recognition of TB and thus on how widespread is the typical clinical syndrome ("classical" tuberculosis)—a productive cough and a chest radiograph showing upper lobe cavitary disease. However, a significant change in the characteristic clinical appearance of TB in HIV-infected patients has been associated with the tuberculosis epidemic, and this change has been a major factor in the number of unrecognized cases of pulmonary tuberculosis and the resulting increase in secondary exposures prior to recognition of the disease.

Characteristics of Tuberculosis in HIV-Positive and Non-HIV-Positive Patients

The demographic, epidemiologic, and clinical characteristics of patients with tubeculosis have significantly changed. In a study reported by Pitchenik in 1987, patients who are HIV positive and have tuberculosis are typically younger in age and black (3), a pattern clearly reflected in New York City.

What has been most challenging for the clinician has been the recognition of tuberculosis in HIV-positive patients, particularly those who have AIDS or have HIV-associated symptomatic disease whose chest radiographs are not "classical" for tuberculosis. Pitchenik has reported a significantly decreased incidence of cavitation in AIDS patients as well as an increase in other radiographic features, such as hilar or mediastinal adenopathy and localized infiltrates involving the middle or lower lung fields. In addition, a decrease in localized infiltrates involving upper lobes and an increase in radiographs without pulmonary infiltrates have been noted. Several patients in the reported series initially had diffuse interstitial linear infiltrates (4). Although this was not significantly different in patients without AIDS, the clinical differentiation of tuberculosis and *Pneumocystis carinii* pneumonia (PCP) may be difficult.

Chaisson and Slutkin (5) note that the x-ray patterns of tuberculosis in patients with HIV infection are related to the patient's CD4 lymphocyte count. In their review, chest radiographs of patients with more advanced HIV disease and tuberculosis show diffuse pulmonary infiltrates (60%), focal consolidation (30%–40%), and intrathoracic adenopathy (25%). In contrast, chest radiographs of patients with earlier HIV infection show cavitary upper lobe infiltrates (45%), lower lung infiltrates without cavitation (20%), and mediastinal adenopathy (20%–30%).

Relative Insensitivity of Acid-Fast Smears in AIDS-ARC Patients. The mycobacterial smear (acid-fast smear) is the usual laboratory study that allows one to make a presumptive clinical diagnosis of pulmonary tuberculosis. In a study reported by Klein of patients with pulmonary TB comparing 38 patients who also had AIDS or ARC to 57 patients who did not and who were not in AIDS-risk groups, 45% of the AIDS-ARC group had a positive sputum smear whereas 81% of the non-AIDS-ARC group had a positive smear ($P < 0.001$) (6). The researchers' conclusion was that acid-fast smears on sputum specimens are relatively insensitive for pulmonary tuberculosis in patients with AIDS and ARC. In addition, in view of the incidence in AIDS patients of infection with atypical mycobacteria, specifically *Mycobacterium avium intracellulare,* a positive smear for acid-fast bacilli may be secondary to atypical mycobacteria rather than *M. tuberculosis.* This only adds to the confusion in the initial diagnosis and thus in proceeding appropriately with isolation and presumptive therapy.

Clinical experience at The Mount Sinai Hospital has included several patients who initially had localized infiltrates and responded to antibacterial therapy, yet whose later laboratory reports noted a positive culture for *M. tuberculosis.* In addition, the coexistence of other opportunistic pneumonias such as *P. carinii* pneumonia with tuberculosis has been well reported (6). We have seen several patients initially diagnosed as having only *P. carinii* pneumonia (negative acid-fast bacilli smears) who responded to antipneumocystis therapy yet later developed either a clinical syndrome of active tuberculosis or merely a positive TB culture.

Approach to HIV-Infected Patients With Respiratory Disease

In order to rationally approach this data and experience, it is recommended that pulmonary tuberculosis be suspected in patients with AIDS or ARC, or who are HIV positive or have risk factors for AIDS, and have chest radiographs

- suggestive of "classical" tuberculosis (upper lobe cavitary disease)
- show mediastinal or hilar adenopathy
- with middle or lower lobe infiltrates and a longer history (several weeks at least) of symptoms than for bacterial pneumonia
- diffuse interstitial infiltrates, especially in conjunction with hilar or mediastinal adenopathy; *P. carinii* pneumonia is not associated with mediastinal adenopathy (5)

Gallium scans with uptake in hilar or mediastinal nodes are also suggestive of pulmonary TB. In addition, tuberculosis should be suspected in patients who are black or Hispanic or are intravenous drug users with these clinical features.

Chaisson and Slutkin report that the symptoms of HIV-positive and of HIV-negative patients with tuberculosis are comparable: fever,

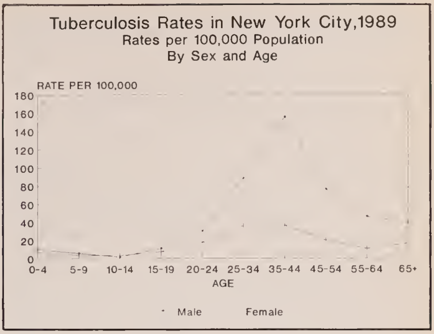

Fig. 2. New York City Department of Health data (ref. 2).

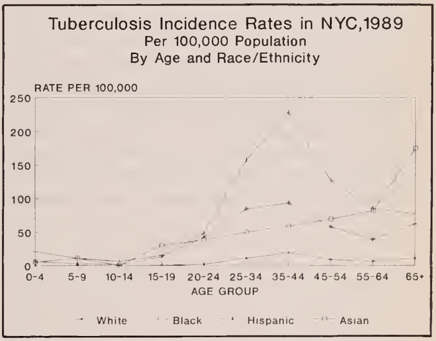

Fig. 3. New York City Department of Health data (ref. 2).

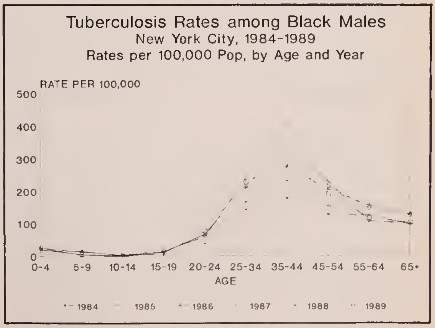

Fig. 4. New York City Department of Health data (ref. 2).

night sweats, weight loss, anorexia, chills, cough, sputum production, and dyspnea. The duration of symptoms is usually at least several weeks; an acute onset is less typical for tuberculosis and more compatible with bacterial pneumonia (5).

All specimens (sputum, bronchoalveolar lavage, transbronchial or open long tissues if available) should be examined and cultured for mycobacteria. Patients should be placed in respiratory isolation until a definitive diagnosis other than tuberculosis is made. If a definitive diagnosis is not made, patients should remain in respiratory isolation. Microbiology laboratories should ideally supply acid-fast smear results daily. In addition, newer methods of identification of mycobacterial species, including BACTEC culture system (Johnston Laboratories, Towson, MD) (5) with gene-probe identification method, will allow identification as early as two weeks rather than the standard six to eight weeks required for earlier methods.

The resurgence of tuberculosis in the United States, particularly in urban areas, has had a tremendous impact on hospitals, including an increase in the number of patients with TB admitted and treated, and a rise in secondary exposure. Efforts to prevent exposure, including heightened suspicion for and earlier diagnosis of pulmonary tuberculosis and the implementation of isolation for patients not definitively diagnosed, will help decrease the spread of the disease. Recognition of the changing demographic patterns of TB associated with HIV infection (particularly in inner-city populations) and of the clinical and chest-radiograph findings described are crucial in preventing the spread of TB to hospital staff and hospital patients as well as the ability to institute treatment earlier to such patients.

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Influenza:

A Serious Epidemic Disease That Can Be Prevented

Stephen G. Baum, M.D.

EVEN though I am an adenovirologist by training, I have had a long-standing clinical interest in influenza; hence my eagerness to discuss it at a Grand Rounds at Mount Sinai Medical Center, and in adapting that talk for this publication. But discussing influenza at Mount Sinai, long a citadel of influenza research, is a case of bringing colds to Newcastle, Kilbourne (1), Schulman, and Palese being the world-renowned influenza virologists they are.

We all currently are devastated by the effects of AIDS, particularly because of its effects on young people. In fact, influenza has been far more lethal for centuries, if not millennia. But influenza epidemics are catastrophes that we now can prevent. That is perhaps the most important message I bring in this presentation. We're not doing nearly enough to prevent epidemics that already have killed, and can in the future continue to kill, many more people than AIDS has thus far.

The Italians first coined the word "influenza" in the 16th century to apply to epidemics—the word means "influence" in Italian—because these epidemics were though to be under the influence of planetary motions and the weather. The word was applied specifically to the disease I am discussing in 1743, when an influenza epidemic struck in Europe. Certainly the disease is partially under the influence of weather.

The Clinical Picture

To set the tone for my discussion, a few words about the clinical disease, which is perhaps the least interesting aspect of the information I am trying to impart here.

As the winter approaches, a lot of people will tell you that they've got "the flu." In fact, a number of infectious agents can produce flulike illness. What we're talking about when we say "I've got the flu" is a febrile disease, usually of acute onset, with chills, fever, malaise, and—in the case of true influenza—myalgias more severe than the normal range of symptoms in other febrile illnesses. Cough is also a prominent and frequent complaint. During the fever, which may go up to 104° or 105° F, the symptoms become worse—the cough worsens, and the shedding of virus into the sputum is greatest. Although many of the symptoms, and particularly the myalgias, have been ascribed to viremia, and better-educated patients and some physicians will describe their illness simply as "feeling viremic," in fact most attempts to isolate influenza virus from the blood during acute influenza attacks have been unsuccessful. So whatever may be causing that lousy feeling that people have when they say they have the flu, it does not seem to be due to the circulation of whole virus particles in the blood.

Usually the disease is self-limited, having an incubation period of one to two or three days, rather short in comparison to mycoplasmal infection, which has an incubation period on the order of two weeks. In influenza outbreaks, members of a family or groups at a school all come down with illness within a couple of days, whereas mycoplasmal infection, which can also occur in closed populations, tends to produce outbreaks over a prolonged period.

Adapted from the author's Grand Rounds in Medicine presentation at The Mount Sinai Medical Center on October 10, 1989. From the Department of Medicine, Beth Israel Medical Center and Mount Sinai School of Medicine. Address reprint requests to Stephen G. Baum, M.D., Director, Department of Medicine, Beth Israel Medical Center, First Avenue at 16th Street, New York, NY 10003.

The symptoms of chills, fever, myalgia, malaise, and cough usually end in three to five days with no treatment except the proverbial chicken soup. The vast majority of people who have demonstrably had a serologic rise of antibodies to influenza are minimally ill, and some of them are not clinically ill at all. However, if symptomatic respiratory involvement does occur, as it does in about 5%–10% of all those infected with influenza virus, the condition may progress to a lower respiratory infection.

The best delineation of the various symptoms and syndromes that can occur in this lower respiratory infection comes from patients studied by Louria, Kilbourne, and their colleagues at New York Hospital in the 1957 epidemic (1). In 33 such patients, several syndromes thought to be typical of many influenza outbreaks were described.

Transient Pulmonary Signs Only. Three of the 33 developed brief transient pulmonary signs, tracheobronchitis, or bronchiolitis. Their X-rays were negative. They had a bad cough and all the other usual flu symptoms. These three were generally healthy people to begin with and the mortality was zero out of the three.

Transient Pulmonary Signs, Seeming Recovery, Bacterial Pneumonia. The largest group (15/33 patients) were initially similar clinically: transient pulmonary signs, clearing, the patients doing rather well, and then—about five days to two weeks later—they returned to the hospital with bacterial pneumonia. This clinical picture is typical: an influenzalike illness, followed by bacterial pneumonia. Only one of these patients died.

Although we may carry around in our heads the thought that *Staphylococcus* is the most common cause of postinfluenzal bacterial pneumonia, that is incorrect. Although *Staphylococcus* infection is more common after flu than it is at other times, in fact our old friend (or enemy), *Pneumococcus,* is probably the primary cause of most postinfluenza bacterial pneumonia, and *Hemophilus influenzae* also plays a role.

Transient Pulmonary Signs, Viral Pneumonia. Another group of 6 (of 33) people progressed directly from transient pulmonary disease to full-fledged primary viral influenza pneumonia. In this group, the mortality rate was rather high. Of the 6 patients who developed the syndrome of pneumonia progressing from tracheobronchitis with positive X-rays showing diffuse interstitial pneumonia, 5 died.

This syndrome tended to occur primarily in people who had rheumatic heart disease, hitherto a waning group of patients but now giving some evidence of reemerging. Our collective attribution of the decrease in rheumatic fever to penicillin is probably inaccurate and inappropriate. Probably the rheumatogenic strains of streptococci that were present in the prepenicillin era and that decided to hide for a while are now reappearing. Patients with rheumatic heart disease and rheumatic fever, who once filled entire hospitals in New York state, could conceivably do so again, as may patients with syphilitic heart disease if the current syphilis epidemic continues. A number of patients with primary influenza pneumonia did have rheumatic heart disease; some were pregnant women with rheumatic heart disease, and they seemed to be particularly predisposed to this primary influenza pneumonia. On autopsy the 5 patients who died had hyaline membranes coating their alveoli, which explained the fact that they died in hypoxia.

Today we might attribute the condition of some of those patients to idiopathic adult respiratory distress syndrome, and we are probably missing a good many of the sporadic nonepidemic cases of primary influenza pneumonia.

Concomitant Influenzal and Bacterial Pneumonia. The fourth syndrome delineated in study of the 1957 epidemic (1) occurred in 9/33 patients who had influenza pneumonia and bacterial pneumonia concomitantly, without a hiatus between viral symptoms and bacterial pneumonia. These 9 patients had both flulike syndromes and bacteria culturable from their sputum at the initial presentation; virus was not culturable from their sputum, but they showed a rise of antibodies to influenza virus. In this group, mortality was relatively high (5 of 9).

This combined pneumonia occurred not only in patients with rheumatic heart disease, but also in people who had some other predisposing cardiorespiratory disease. So true influenza pneumonia, whether or not it is complicated by bacterial pneumonia, can have a relatively high mortality rate.

All four of these syndromes are probably occurring all the time, even when no major epidemic like the 1957 outbreak is under way.

Extrapulmonary Complications. Several nonpneumonic complications of flu can arise.

Primary among these is Reye's syndrome. When I was a house officer, I saw one of the first patients with this syndrome, the seventh, eighth, or ninth case reported. In retrospect, it was a really typical case, and nobody, certainly not myself, knew what was going on. The patient had experienced a respiratory infection about ten days preceding the onset of coma; she had encephalitis, hypoglycemia, hypoglycorachea (spinal fluid sugar was 6 mg/dL). The patient recovered spontaneously. Since then this syndrome of encephalitis with low levels of sugar in serum and cerebrospinal fluid following respiratory infection has been reported frequently. Originally it was an autopsy diagnosis, and so the mortality rate was thought to be 100%. The only finding was some fatty vacuolation of the liver and a little brain edema. The mortality remains fairly high, about 40%.

Reye's syndrome has now been described as a postinfectious consequence of influenzal disease, influenza B probably exceeding influenza A as a cause, and also as a complication of varicella. Some data indicate that giving salicylates during either varicella or influenza infection increases the likelihood of this syndrome developing. So aspirin, used as a treatment for a flulike illness or for chicken pox, is contraindicated.

The relationship is hard to understand; the patients have normal salicylate values. The only chemical findings that help in Reye's syndrome are that the serum ammonia level is usually high and the ornithine transcarboxylase levels are usually low. Those values mirror one another, but as far as I can tell, nobody really understands what's going on in Reye's syndrome.

Other extrapulmonary complications include myositis, encephalitis, pericarditis, myocarditis, and the possibility of Guillain-Barré syndrome, which I discuss below. The causal relationship between influenza and these extrapulmonary manifestations is also hard to pin down, and I am not sure that it exists. The virus is usually not isolated from any affected organs.

The Epidemiologic Picture

Influenza has plagued people for a long time in three ways: as sporadic disease, as epidemic disease, and as pandemic disease.

In temperate climates, influenza peaks in the wintertime, but in some tropical climates it may peak in summer. The common denominator appears to be crowding; tropical summers are rainy seasons, and people may be clustering in their huts, the way we sit in auditoriums, coughing on one another. In either case, it certainly is a disease with a seasonal preponderance.

There are three serotypes of influenza virus and, with the usual creativity of microbiologists and other investigators, these have been named A, B, and C. Quite clearly type A is the one predominantly related to epidemics and pandemics.

Flu vaccine protects 75%–80% of those vaccinated, yet only about 20% of high-risk persons are being vaccinated each year.

Epidemics. A great deal can be learned from examining some of these epidemics in detail. Type A epidemics generally occur every two to three years.

A plot of "excess" deaths (Fig. 1) in any given year ("excess" death being a term developed by the Centers for Disease Control, but I suspect it was invented by the Pentagon) compares the number of deaths in a given year against the norm for many years. The peaks of excess death occur in the years of influenza epidemics. The deaths are due to pneumonia and cardiopulmonary collapse, and those deaths are pretty directly attributable to influenza activity by autopsy reports and death certificates. So this disease can kill a lot of people and has repeatedly been demonstrated to do so.

Pandemics. Major influenza pandemics—a pandemic being an epidemic occurring in more than one locale, and in the case of influenza usually worldwide—have in the past appeared at about 10-year or 15-year intervals (Fig. 2). This cycle is breaking down in this century, for reasons I discuss below. Both epidemics and pandemics of influenza have generally been due to type A influenza. Type B influenza has been associated with outbreaks in schools and other closed populations, like *Mycoplasma* pneumonia outbreaks; type C influenza causes more sporadic disease, primarily in children, and often goes undiagnosed.

The 1918–1920 Pandemic. Pandemics that have occurred in this century yield important insights into influenza. During the notorious 1918–1920 pandemic, called at the time the "Spanish flu" epidemic (Fig. 2), the deaths of some 20 million people throughout the world were directly attributable to influenza. Note that this huge number of deaths took place over a three-year period and contrasts strikingly with the 50–60,000 AIDS-related deaths that have occurred in the past ten years.

The second interesting thing about that pandemic, after the enormous number of deaths it caused, is that the mortality curve was not a V shape but a W shape. In almost every infectious disease epidemic or pandemic that has been studied, the very young die, and the very old die, making a V-shaped mortality curve. In the 1918–1920 pandemic, the primary group that died from influenza were people in their twenties and thirties, making a W-shaped curve.

Testimony from Katherine Anne Porter's short story "Pale Horse, Pale Rider," set in the period, for example, leaves a reader with the impression that a person in this age group had two "choices"—either dying of influenza or having been killed in World War I. Chronicles of the time show that physicians would get a message (telephones were not widely in use) to come see a patient who had a respiratory illness and fever. The doctor would be busy taking care of other patients, he'd eventually make the house call (house calls were widely in use), and he would find the patient, who was 20 years old, dead in bed.

The third somewhat unusual feature of the 1918–1920 pandemic was that from the sputum of many people (there was no virology then, but there was bacteriology), a gram-negative coccobacillary organism—a *Hemophilus*—was grown. In fact this organism, *Hemophilus influenzae,* was so named because it was thought to be the cause of the 1918–1920 pandemic. It has not been a major bacterial superinfecting agent in epidemics subsequent to 1918, but it would seem to have been extremely common in those days.

The final unusual characteristic of this pandemic was the relatively high incidence of the encephalitis called von Economo's or lethargic encephalitis, and many people who survived that encephalitis developed a Parkinson's-like syndrome later in life. I do not think the majority of Parkinson's disease is due to influenza, but in this particular instance there is an epidemiologic tie between having developed encephalitis, surviving it, and developing Parkinson's disease later on.

An important point about this pandemic is that no science of virology existed in 1918, so no one knows with certainty what virus caused it. But when virology developed and careful serologic studies of influenza began, researchers found that people who were alive in 1918 had antibodies to so-called swine influenza virus, and that people who were born after 1923 generally did not have antibodies to swine influenza virus. So the implications are relatively strong that the 1918 epidemic may in fact have been caused by the swine influenza virus. (I discuss the relevance of that fact below.)

The 1957 Pandemic. I was one of the 80 million people in America who were sick with influenza during the so-called Asian flu epidemic of 1957 (Fig. 2). Eighty million people in the United States represents an attack rate of about 50%. And in that year alone there were 60 thousand extra ("excess") deaths in the United States directly attributable to influenza–again, a number of deaths equal to, or in excess of, all the people who have died of AIDS thus far.

So many people got sick in 1957 because very few had antibodies to the causative strain of influenza; it seemed to be appearing for the first time. But there was one group of people, normally susceptible to influenza infection, who did not seem to contract it: people aged about 70 years were spared, largely if not uniformly. People of that age had been around in 1898. So it would appear that the 1898 epidemic may have been caused by a virus similar to the one that was resurfacing in 1957, and that those people who had, in fact, survived the 1898 epidemic were somehow relatively or specifically immune to the virus when it showed up again in 1957.

The Virologic Picture

Antigenic Drift and Antigenic Shift. Kilbourne was influential in unraveling part of the mystery: that strains of type A share antigenic determinates with strains isolated in the years just before, so that the 1989 type A is similar to the 1988 and the 1987 type A strains. These strains may differ by one or more surface amino acids that confer antigenic specificity to the virus, a difference resulting from mutation in the RNA genome of this virus. Thus each year the virus seems to change just a little bit from the year before, due to spontaneous mutation. This year-to-year change has been called antigenic drift.

Epidemics occur as antibodies to the virus prevalent in previous years wane, yielding a susceptible population. When the subtle year-to-year drift becomes sufficient to render prevalent antibodies nonprotective, epidemics occur.

Every once in a while, a major antigenic change, an antigenic shift, occurs in the virus. When it occurs, antibodies in a large number of people in one locale, or throughout the world, no longer recognize this virus as something seen before, and the result is not an epidemic, but rather a pandemic.

This second phenomenon, antigenic shift, results from genetic reassortment in the virus. Influenza viruses are unusual in that they can produce what appear to be new virions, by reassorting their genes. Much of this reassortment

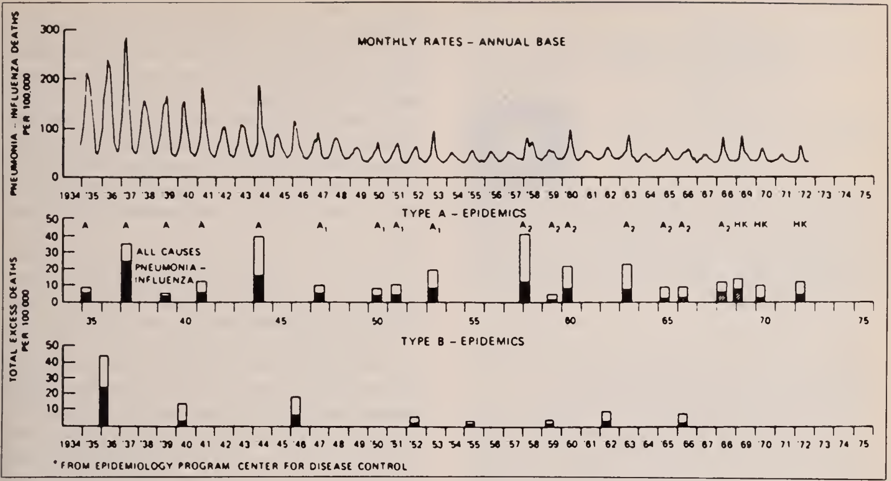


Fig. 1. Pneumonia and influenza death rates and excess deaths (deaths in a given year over the norm for many years) as they relate to influenza epidemics and pandemics. HK, Hong Kong virus. Reprinted from Centers for Disease Control. Influenza-Respiratory Disease Surveillance Report No. 88. U.S. Department of Health, Education and Welfare, Public Health Service 1973.

phenomenon has been worked out at Mount Sinai, but it is still not really understood very well.

Thus antigenic drift occurs year after year; when enough changes build up, an epidemic occurs. Then when an apparently new virus comes along, and no one is immune, a major world pandemic is upon us.

How Do New Viruses Emerge? Several theories have been devised to explain how new viruses might emerge. None of them gives all the answers, but one that is particularly intriguing involves animals, notably pigs, as reservoirs.

Nowhere do pigs and humans resemble one another more than in their susceptibility to various infections and in their immunologic systems. One of the theories to explain the emergence of new viruses is that the human population becomes relatively immune to a strain of virus that is widely passed from person to person, but at some point that strain enters an animal reservoir. Birds, pigs, and other animals can harbor the virus for years, even decades. When another strain of influenza virus becomes epidemic among humans, that second strain is transmitted to the same animals carrying the first strain. This may yield a reassorted virus that can then reenter the human population; decades later, a population never challenged by this recombined or reassorted virus is totally susceptible, and a pandemic will occur. Only those people who survived the first epidemic may be resistant to this apparently new, but actually reemergent, virus.

Epidemiologic support for this animal-reservoir theory comes from the fact that many flu epidemics begin in Asia, particularly in pig-raising areas of Asia, before spreading throughout the world.

That there are animal reservoirs for influenza suggests that we are not likely to eradicate the disease; if we do so, it will only be with great difficulty. In this, influenza differs from smallpox. There is no nonhuman reservoir for smallpox, so

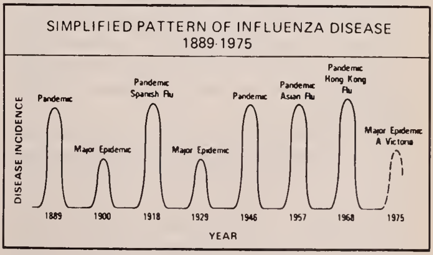
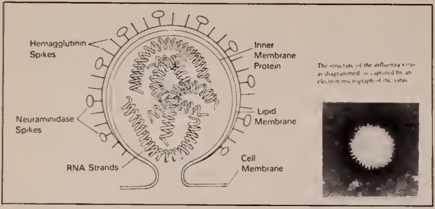


Fig. 2. Epidemiologic pattern of influenza epidemics and pandemics. Reprinted from National Institutes of Health, National Institute of Allergy and Infectious Diseases. Report of the Director, 1978.



The structure of the influenza virus as diagrammed is captured by an electron micrograph of the virus.

Fig. 3. (Left) Schematic diagram of influenza virion budding from surface of infected cell. Studded projections are antigenic determinants. (Right) Electron micrograph of influenza virus particle. Reprinted from National Institutes of Health, National Institute of Allergy and Infectious Diseases. Report of the Director, 1978.

that the current worldwide human immunization policy can eliminate it from the earth.

Why Do Influenza Epidemics Stop? It is not clear why influenza epidemics stop. They tend to stop long before the susceptible population is infected, and we really do not understand where the virus is from one season to the next. For instance, in the temperate zone, as I mentioned, the influenza season is anywhere from December through April. After April it is very difficult to culture this virus from anybody—but the virus may reappear again in cultures the following December.

Virology

This antigenically variable respiratory virus is rather pleomorphic or close to amorphic; it assumes many different shapes (Fig. 3). Its surface is studded with projections. Inside is single-stranded nucleic acid, single-stranded RNA, occurring as eight pieces or segments. The fact that the genome comes in pieces is thought to be responsible for easy reassortment. In other words, infection of a single cell with two different virus strains can easily lead to some of the genetic material from each strain being packaged together in new viral progeny that have some of the characteristics of each of the parent viruses. This reassortment would be manifest by new antigenic determinants (the studded projections) on the virus surface.

Two of these projecting proteins, hemagglutinin and neuraminidase, are of primary interest in the epidemiology and pathophysiology of influenza.

Hemagglutinin is so called because it is the protein responsible for the capacity of the influenza virus to agglutinate red cells in vitro: influenza virus in a test tube with the right kind of red cells produces clumps. However, the business of this virus is not to clump red cells in a test tube, but rather to infect respiratory cells, and the first step in any kind of virus infection is adsorption or attachment. The virus has to attach itself to a cell before it can get inside. It is believed with a good deal of certainty that the role of the hemagglutinin is to attach the virus to the surface of the cell as the first step in viral replication. Evidence that this is the case is that antibody to hemagglutinin will prevent the attachment of the virus to cells, so that a plaque assay, which measures how many viruses have hit how many cells, will reveal that if antihemagglutinin antibody is added to virus before infecting those cells, no plaques will be produced.

Neuraminidase is perhaps an even more interesting cell surface component. Neuraminidase has also been called receptor-destroying enzyme because, purified, it has the capacity to destroy a number of receptors on a number of different kinds of cells. If red cells are agglutinated with influenza virus and allowed to sit a while, they will disaggregate and can never be agglutinated again. The role of neuraminidase is thought to be the breakup of that aggregation. But, just as the role of the virus is not to agglutinate red cells, the role of neuraminidase—and this is teleologic, but I think accurate—the role of the neuraminidase is certainly not to break up red-cell aggregations in a laboratory. Influenza virus is an enveloped virus, and the envelope is composed of modified cell membrane. The virus gets out of the cell not by causing an explosion, and bursting out tens of thousands of new particles, but rather by budding the virus off the surface of cells (Fig. 3). At the penultimate step before the virus can actually free itself from one cell and get to another, it has got to be released from the first cell. Presumably the role of the neuraminidase is to do just that: to cleave the bonds between the emerging new virus progeny and the cell from which those progeny are emerging. In fact, if the plaque assay is repeated, adding antibody to neuraminidase rather than to hemagglutinin, the plaques do not decrease in number but rather decrease in size. The size of the plaque reflects how many cells surrounding the initial infected cell get infected by the progeny of the initial infection themselves. So if the action of neuraminidase is stopped by adding antibody, the virus can get into the original cell but has trouble shedding from that cell and therefore trouble entering other cells. In addition, in vivo, the neuraminidase may play a role in liquefying mucus in the respiratory tract and enabling the virus to closely approach epithelial cells.

The first step in working on this virus was being able to grow it in animals. Ferrets develop influenza when their noses are blasted with influenza virus; that was the initial experimental evidence in 1933 that allowed people to work with this virus (2). Subsequently it was grown on the alantoic membrane of embryonated eggs, and finally in tissue culture cells. Both primary cells and continuous lines of cells can serve for the growth of influenza virus.

Prevention

Humans, in the course of influenza infection, make antibodies to many components of the virus. It is thought that the antibodies to the hemagglutinin are the most protective antibodies we make. The antibodies to neuraminidase are protective to a lesser extent; antibodies to the core nucleoproteins do not protect much, although they can be used as a measure that we have been infected.

Presumably these antibodies can protect us against infection with the identical virus for the rest of our lives; the fact that in 1957, 70-year-olds did not get Asian flu, caused by a virus they may have contracted in 1898, tells us that live virus infections, particularly of influenza, may give us lifelong immunity. An emerging theme in viral immunology is that killed virus vaccines give relatively short protection, but live virus vaccines and natural infection with many viruses (mumps, measles) probably give lifelong protection, presumably because a low level of viral replication, and thus continued antigenic stimulus, is going on in the body for every virus that has ever infected the person.

Therefore, it is not so remarkable that herpes virus, for instance, remains latent in dorsal root ganglia. The most remarkable thing about the herpes virus group is, in fact, that the virus can be reactivated, to produce varicella zoster after chickenpox or repeated cold sores after primary herpes simplex.

Modalities for Prevention. The spread of influenza these days can be rapid; the virus can move from Asia to America via plane in twelve to fourteen hours, shortening from months to hours the time an influenza epidemic can take to traverse the world and become pandemic. This speed makes prevention of influenza, which can kill 20 million people in two years, more imperative than ever.

And prevention is possible. Your grandmother told you to wear a scarf in the wintertime; that may be one preventive, although I tend to doubt its efficacy. The Russians prefer wearing a clove of garlic around the neck. Because crowding is the common denominator for spread of this infection, a clove of garlic may indeed have an effect—it keeps people from getting too close to one another.

The major reason for the low vaccination rate is physician apathy.

Chemoprophylaxis with Amantadine. One of the modalities for preventing this disease is not a vaccine, but rather a drug, amantadine (Symmetrel). This drug works only against influenza type A. It has no or very little effect against type B or C. Such serotype-specific activity might lead one to think that the drug plays a role either in preventing the virus from attaching to cells, which is a serotype-specific activity, or in penetrating the membrane, also a type-specific activity. However, the drug appears to play a role in the next step in viral replication, that is, uncoating of the viral ribonucleic acid.

In order for any virus to replicate, it has to partially peel off the protein coat, thereby exposing its nucleic acid, so that the nucleic acid can then code for more protein and more nucleic acid. Amantadine appears to prevent that uncoating step. It is about 75% or 80% effective in preventing influenza. It must be given before an epidemic strikes and during the total duration of the epidemic, since it has no lasting effect; it is excreted unchanged through the kidney, and several days after stopping it the patient is no longer protected. So prophylactic use of this drug should probably be saved for those patients who are at high risk, who missed being vaccinated, once an epidemic has struck. But amantadine prophylaxis is not, and should not be thought to be, a substitute for vaccination. With vaccination its effect may be additive.

The recommended dosage is 200 mg/day. At this dose the drug has moderate side effects in many people, unfortunately greatest in people aged over 65 years—just the population most in need of protection. The side effects are primarily in the central nervous system: insomnia on the one hand, lethargy on the other, confusion in the middle. It has been suggested that doses of 100 mg/day instead of 200 mg/day may give the same protection with lesser side effects (3), based on the fact that rimantidine, a Canadian drug similar to amantadine but not so far released in the United States, has fewer side effects but is more poorly absorbed. The theory is that because the level of the drug in blood is lower, fewer side effects are produced.

Another suggested role for amantadine, one not yet proven to my satisfaction, is that the drug may abort or shorten the clinical course in unvaccinated people who have developed type A influenza.

In the next major epidemic of influenza type A in this county, the therapeutic effect of this drug can be tested. When it was tried in prisoner "volunteers," it was shown to somewhat decrease the duration of their illness. Unfortunately, the study did not include a good aspirin control, and probably no study should include an aspirin control, given the side effects of salicylates in influenza.

Although I am not yet convinced that the drug has any therapeutic role, the assumption that it might have is perfectly reasonable, because viral diseases are the result of multiple rounds of replication of the virus, and if one could stop the replication the body would clear the virus, presumably shortening the disease, and perhaps preventing the more serious complications, including death.

Vaccination. The primary mode of preventing the disease is vaccination. Several high-risk populations identified via previous influenza epidemics need protection. Those populations are increasing yearly, but only about 20% are being protected—despite the high rate of protection offered by vaccination, which is 75%–80%. The major reason for the low vaccination rate appears to be apathy, physician apathy, about immunization. Patients' fear of the side affects of influenza vaccine is probably the second, and lesser, reason for the low rate of vaccination. Many physicians are unaware that amantadine may be of any use at all.

High-Risk Candidates for Vaccination. The current recommendations of the CDC (4) on high-risk populations that should be vaccinated for influenza—and these same groups are candidates for amantadine prophylaxis if vaccination has not taken place—encompass the following:

- Adults and children with chronic cardiopulmonary disease (as identified in the 1957 epidemic).
- Adults and children with metabolic disorders such as diabetes and immunosuppression, including human immunodeficiency virus (HIV) disease. Killed or inactivated vaccine is not a risk to an immunocompromised patient.
- People with hemoglobinopathies or with renal dysfunction, namely all dialysis patients.
- Every resident of nursing homes and other chronic care facilities. These people are the aged, who are often immunocompromised in some way.
- Healthy persons over 65 years old.
- Children (and probably adults) taking aspirin as long-term therapy. A disease that has a sequel as devastating as Reye's syndrome must be prevented.
- Healthcare workers who have contact with high-risk patients. That means immunizing all nurses, all medical students, all physicians. Such immunizations are simply not being done, but that is a mistake; we should be immunizing healthcare workers.
- Individuals who provide essential community services.
- Pregnant women. If one can avoid vaccination in the first trimester, good, but after the first trimester, there should be no problem. A killed vaccine, such as the influenza vaccine, should not pose a problem even in the first trimester, but drug companies are cautious about any immunization in the first trimester.
- Individuals infected with HIV; again, killed vaccines are not contraindicated.
- Travellers to the Southern Hemisphere, the tropics, where influenza may occur outside the September-to-April pattern of the Northern Hemisphere.

Vaccine. The vaccine must be strain specific, because protective antibodies that are formed against the hemagglutinin and neuraminidase do not effectively crossreact; they do not really protect all that well against similar but nonidentical influenza viruses.

Work by Kilbourne seems to show that probably only a relatively limited number of strains of type A influenza are possible. This would make the production of a finite number of vaccines potentially protective against all influenza. But the job is somewhat complicated by what Fazekas de St. Groth has cleverly dubbed "original antigenic sin" (5). It has been shown that someone infected with a particular strain of type A influenza virus who is later vaccinated with a similar but different strain will have a predominant antibody response not to the vaccination virus given today, but rather to the closely related virus first experienced. I am not certain whether that finding plays a real clinical role in protection.

The only major contraindication to vaccinating all members of high-risk groups is egg allergy. The vaccine virus is grown on eggs, and although the subunit vaccine is very highly purified, some egg protein may remain. Other side effects are generally quite mild: a little pain in the arm, possibly a little fever. Those people who claim that two days after vaccination they got the flu may in fact have gotten the flu, but not from the vaccine, because the vaccine is incapable of causing flu.

Three intramuscular preparations are available: whole-virus vaccine, split-virus vaccine, and purified subunit vaccine. The whole virus is grown in culture, on eggs, and then can be used as vaccine, or split up into its components and used as split-virus vaccine. Alternatively, the nucleoproteins are thrown away and the essential subunits, which are the neuraminidase and hemagglutinins, are purified to prepare subunit vaccine.

The primary vaccines in use today are either whole-virus or subunit vaccines. The subunit vaccine is recommended for children because the side effects are fewer. Children under 12 should get two shots; people over 12 should get one shot of vaccine. Each must be revaccinated each year, for two reasons. First, neither killed nor inactivated subunit vaccines give prolonged protection. Second, influenza strains vary from year to year by antigenic drift, and vaccination in one year, even if antibodies to that vaccine were to remain at high titer, would not necessarily protect against the strain prevalent in the current year.

The 1990–91 Vaccines. The 1990–91 vaccines (6) contain components of two type A viruses: A/Singapore/6/86 (H1N1) and A/Shanghai/16/89 (H3N2). The suffix numbers after the letters H and N identify the antigenic variety of hemagglutinin and neuraminidase. There are three different human types of hemagglutinin, labeled H1, H2, and H3 (there used to be five, but two were subsumed into type 1), and two different kinds of neuraminidase, N1 and N2. These can be found in mixtures on the surface of the virus. A virus is therefore described by type (A, B, or C); by where it was first isolated (Taiwan, Shanghai); by when it was isolated; and by the makeup of its hemagglutinin and its neuraminidase. So A/Singapore/6/86 (H1N1) indicates that the virus has on its surface hemagglutinin 1 and neuraminidase 1; A/Shanghai/16/89 (H3N2) indicates the virus has on its surface hemagglutinin 3 and neuraminidase 2.

In the 1990–91 vaccine there is also a type B virus, B/Yamagata/16/88. There are no hemagglutinin or neuraminidase typings on type B viruses, so no suffixes are necessary. Vaccines for the last decade have contained two type A and a type B, each of the three generally changing from year to year, so a current vaccine must be used.

Killed vaccine, which is what influenza vaccine is, is not a risk to an immunocompromised patient.

Some experimental vaccines are under investigation. These are live vaccines, principally to be used intranasally to produce IgA antibodies, but they are far from being on the market at the moment.

Timing of Vaccination. The optimum time to vaccinate is late October or early November. Vaccination should not be too early because immunity may wane by May, particularly in old patients, although influenza may still be around. From mid-October on is the time you should be vaccinating just about every patient. The patients who are candidates for flu vaccine are also often candidates for pneumococcal vaccine (pneumovax), which can be given simultaneously; the two vaccines to not interfere with one another.

Caution on Theophyllin Levels in Blood. Some information in the literature (7) indicates that vaccination with flu virus, for reasons that are not very well understood, can raise the blood level of theophyllin. This is theoretically important because asthmatics are patients whom you might want to be vaccinating. Vaccination can also raise the levels of warfarin. Although of theoretic importance, these findings may not be clinically relevant. That is, the levels do not go sky-high and probably do not need to be adjusted, but those patients being treated with theophyllin should be watched carefully for toxicity.

The Nonepidemic of 1976. One threatened epidemic that turned out to be a nonepidemic offers an important lesson: the nonepidemic of 1976. In 1976 some 400 cases of influenza were recognized at Fort Dix, NJ, and four deaths were reported. A major uproar ensued because the virus isolated from the Fort Dix patients was swine influenza virus, an H1N1 virus. In 1976 the perceived threat was that nobody had experienced infection with swine influenza in recent years, and that this virus was presumed to have been the cause of the devastating 1918–20 pandemic in which 20 million people died. I say "presumed" because nobody knows what caused that epidemic disease; we know only, as I mention above, that people born by then have antibodies to swine flu, and those born later do not. Those 400 cases and those four deaths resulted in 45 million people being vaccinated in the United States. I think it was totally appropriate to get worried and to make, to distribute, and to store the vaccine. In retrospect it does not seem all that appropriate to have given vaccine to that many people, because about one in 100,000 people who received that vaccine developed Guillain-Barré syndrome—ascending motor paralysis—and about one in ten of those persons died.

In the meantime, the epidemic never happened. No one knows why. Perhaps swine influenza virus had lost some of its transmissibility. We do not know, and no one can know, that what did not happen in 1976—pandemic spread of swine influenza—won't indeed happen the next time. We are still, most of us, susceptible to that virus. We don't know whether, if it were to return in 1994, it would have the same devastating effect it had in 1918. Yet we are left terribly vulnerable for the future, because no politician in his or her right mind is going to back a major swine influenza virus vaccine program with the knowledge of what happened, and what didn't happen, in 1976. The political judgment is likely to be "A vaccine that produced Guillain-Barré syndrome? No way." The reasons why the swine vaccine produced Guillain-Barré syndrome are still not known. So we remain in a twilight zone, highly vulnerable to what may be a devastating virus, and politically probably not in a position to vaccinate that many people again.

The problem with that memory of 1976 is that it is probably the factor preventing many of you from vaccinating your patients, and perhaps a factor preventing some of your patients from wanting vaccine. But Guillain-Barré syndrome following influenza vaccine has never been recorded in the 13 years of vaccination since 1976, and really should not be used as a reason for not vaccinating people.

Questions and Answers

Richard Gorlin: Thank you very much, Dr. Baum, for this timely discussion.

Dr. Kilbourne, do you have any comments or thoughts, as one of the pioneers in this field, that you would care to impart to us?

Kilbourne: Let's go in reverse order about 1976. I think it's worth recalling, concerning the political implications of the actions taken there, that then Secretary of Health Califano fired Dave Sencer, who was then head of the CDC, immediately after he came into office, an action related, I think, to the management of the swine flu challenge. When influenza A of another type appeared in some nursing homes in Florida, he reinstituted influenza vaccine immediately. So it's a matter of the perceived and the real threat.

> From mid-October on, physicians should be vaccinating just about every patient.

The other point is, I believe, that if you immunize 40 million people with anything—egg albumen, Drano, whatever—a certain incidence of reactions will show up if you follow that group intensively. Prospective surveillance reveals all kinds of things. I think the evidence is not in that the swine influenza virus is any more pathogenic in terms of Guillain-Barré syndrome than any other influenza virus. So I think that the experience subsequent to that time simply reflects the fact that we haven't been immunizing 45 million people a year. I mention that because I think that still remains as a deterrent in some people's mind to immunization. In my view it's close to malpractice if you do not immunize people who have backgrounds of pulmonary and cardiac disease.

In that connection, the pregnant woman should I think be vaccinated in any trimester to prevent the possibly lethal effects that can occur in the third trimester. The reason for the vulnerability of pregnant women in the third trimester is not completely clear, but I think it is probably more related to cardiopulmonary dynamics than to any endocrine effects. Pregnant women have the same kind of syndrome as do patients with rheumatic cardiac disease, so pregnant women, even those without rheumatic heart disease, should be immunized.

Meyers: What about the effect of exercise on susceptibility to contracting influenza?

Baum: We know it has a role in what happens after polio infection, and we know it has a role in what happens after some coxsackievirus and other enterovirus infections. I'm not clear that it plays any role in what happens after you get influenza. Dr. Kilbourne, are you aware of exercise relating to severity of influenza? [presumably received a negative nod] No, I'm really not.

Question: Does exposure to cold play a role in susceptibility to influenza?

Baum: That field is very difficult to pin down. As you well know, almost every study of cold temperature and respiratory virus infection—having Naval recruits sit on blocks of ice with fans blowing on them, for example—has failed to reveal any connection between being cold and getting a cold. Nonetheless, we all adhere to what our bubbas told us to do—wear a scarf and boots when you go out in the cold. I'd be happy to tell Dr. Kilbourne he's wrong, but I would never tell my bubba she was wrong. So I really don't know whether cold or exercise plays any role.

Gorlin: Thank you very much, Dr. Baum and Dr. Kilbourne, for joining with us.

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Endocrinologic and Metabolic Manifestations of the Acquired Immunodeficiency Syndrome

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Abstract

The endocrine abnormalities associated with acquired immunodeficiency syndrome (AIDS) are reviewed. These include adrenal insufficiency, hyporeninemic hypoaldosteronism, panhypopituitarism, hypogonadism, and alterations in thyroid function tests. AIDS-related infections or neoplasms may lead to hypercalcemia, whereas malabsorption may cause hypocalcemia. The possibility that AIDS-associated cachexia and hypertriglyceridemia may be caused by cachectin (tumor necrosis factor) is discussed, along with possible therapy for cachexia with megestrol acetate. Ketoconazole, sulfonamides, and pentamidine have specific, potentially deleterious metabolic effects when used in AIDS patients. Because treatment of endocrinological abnormalities of AIDS is often effective, improved diagnosis and appropriate therapy of these abnormalities will result in improved quality of life and, possibly, longer survival of patients with AIDS.

ACQUIRED immunodeficiency syndrome (AIDS) is a disease that currently affects more than 172,000 persons worldwide, almost 100,000 of them in the United States alone (1). Furthermore, approximately one million persons in the USA are infected with HIV and are therefore at high risk of developing AIDS (2). At the present time, the only treatment that has been shown to be effective in prolonging the survival of patients with AIDS is the antiviral drug azidothymidine (AZT) (3). It is our belief, however, that treatment of various endocrinologic and metabolic manifestations of AIDS may also prolong survival and improve the quality of life of persons with AIDS.

Multiple endocrinologic abnormalities have been reported in association with AIDS and are apparently due to the disease. In addition, certain medications commonly used in the treatment of patients with AIDS may sometimes cause metabolic or endocrine abnormalities. The endocrinological aspects of AIDS, in spite of their variety, have received relatively little attention in the medical literature (4). It is the purpose of this review to summarize the literature and the authors' unpublished observations on endocrinologic and metabolic manifestations of AIDS, in a format that will be useful for clinicians. It is our hope that improved alertness to the possibility of such manifestations will lead to their earlier diagnosis and treatment. Because such treatment is usually quite effective, it can lead to an improved quality of life and possibly to longer survival of persons with AIDS.

Endocrinologic Abnormalities in AIDS

Adrenal Insufficiency. Adrenal insufficiency is perhaps the most important endocrinological manifestation of AIDS (5–9). The pathogenesis of adrenal insufficiency in AIDS is not always clear; unexplained necrosis of the adrenal glands and

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necrosis resulting from infection with cytomegalovirus, fungi, or mycobacteria have been described (9, 10).

Adrenal insufficiency may be difficult to diagnose in patients with AIDS because its manifestations are often similar to some of the manifestations of AIDS itself or of its complications, such as septic shock. Patients may have fever, hypotension, confusion, abdominal pain, nausea, or vomiting. The presence of hypoglycemia, hyperkalemia, or hyponatremia should lead to a suspicion that adrenal insufficiency may be present. The diagnosis should be strongly suspected if one demonstrates a low or normal random serum cortisol level in a maximally stressed, "sick" patient, and can be definitively confirmed by a rapid ACTH stimulation test (11).

Treatment involves "fluid resuscitation" (best accomplished with normal saline), administering parenteral "stress doses" of glucocorticoids initially (for example, 300 mg of hydrocortisone over a period of 24 hours), and oral maintenance therapy once the patient is stable (25 mg of cortisone acetate in the morning and 12.5 mg in the evening). Some patients may also require long-term mineralocorticoid replacement (for example, fludrocortisone, 0.1 mg/day). This treatment is quite effective and results in marked improvement in the patient's condition within hours of its initiation.

Hyporeninemic Hypoaldosteronism. Adrenal insufficiency should be differentiated from hyporeninemic hypoaldosteronism (HHA), which we have reported in patients with AIDS (11). Patients with this syndrome may have orthostatic hypotension and unexplained hyperkalemia. Hyponatremia and mild metabolic acidosis may also be present. The diagnosis can be established by demonstrating a subnormal response of plasma renin and aldosterone to four hours of stimulation by upright posture plus mild dehydration. The dehydration can be achieved by injecting 40–80 mg of furosemide intravenously. This elaborate test, however, is seldom required. Instead, one can perform a rapid ACTH stimulation test in a patient with unexplained hyperkalemia and orthostatic hypotension. If the cortisol response is normal, thus excluding adrenal insufficiency, it is reasonable to attribute the patient's hyperkalemia to HHA.

The pathogenesis of HHA in AIDS, or in other conditions in which HHA is commonly seen (such as diabetes), is unknown. Damage to the juxtaglomerular apparatus, sympathetic insufficiency, atrial natriuretic factor abnormalities, and other mechanisms have been proposed (11). An intriguing possible cause of selective aldosterone deficiency in AIDS could be an excess of cachectin, also called tumor necrosis factor (TNF), which can selectively suppress aldosterone synthesis (12). As we discuss in more detail below, circulating TNF levels are elevated in some patients with AIDS (13).

It is important to distinguish HHA from adrenal insufficiency, because the treatment for these conditions differs: adrenal insufficiency is a life-threatening condition that requires therapy with glucocorticoids; such therapy may be detrimental in an immunosuppressed patient. The non-life-threatening HHA is treated with mineralocorticoids: fludrocortisone (0.1 to 0.2 mg/day orally) is very effective in normalizing serum potassium and sodium; orthostatic hypotension dramatically improves so that the patients are no longer bed-ridden.

Panhypopituitarism. Panhypopituitarism is another endocrinological abnormality that has been reported in AIDS, in a patient with central nervous system toxoplasmosis (14). Endocrinologic testing demonstrated deficiencies of ACTH, growth hormone, TSH, and gonadotropins. Autopsy revealed a necrotic anterior pituitary gland, with a sparse lymphocytic infiltrate and no demonstrable Toxoplasma organisms or viral lesions. The posterior lobe of the pituitary was normal. The incidence of hypopituitarism in AIDS is unknown. When pituitary insufficiency is present, adequate replacement with glucocorticoids, thyroid hormones, and sex steroids (if desired) is indicated.

Hypogonadism. Hypogonadism is present in many male patients with AIDS (15, 16), and testicular atrophy has been reported as an autopsy finding (10). Gonadotropin levels are appropriately elevated in some patients, suggesting that testicular failure is the primary cause of the hypogonadism in them. In other cases, gonadotropin levels are depressed or inappropriately normal, suggesting hypothalamic or pituitary involvement. Treatment of hypogonadism involves replacement therapy with testosterone, when desired by the patient.

Hyperprolactinemia. Hyperprolactinemia has been described in patients with AIDS, as well as in clinically healthy HIV-infected individuals (15, 16). The pathogenesis of this abnormality is also unknown. It is possible that hyperprolactinemia in AIDS is due to a nonspecific effect of a systemic illness: prolactin (like cortisol) is released in response to stress. Thus, prolactin is often elevated in a critically ill patient. However, as HIV infection in the central nervous system itself has been clearly demonstrated, hypothalamic dysfunction resulting in deficiency of prolactin-inhibiting factor (dopamine), and therefore hyperprolactinemia, cannot be entirely excluded.

Cachexia and Hypertriglyceridemia. Yet another striking metabolic abnormality described in patients with AIDS is cachexia. Profound weight loss is an extremely common feature of AIDS. Although its pathogenesis is unknown and is likely to be multifactorial, various investigators have postulated that cachectin, also known as tumor necrosis factor (TNF), may be involved. Elevated levels of circulating TNF in patients with AIDS have been reported by some investigators, whereas others have found these levels to be normal or low (13, 17–19). It is possible that increased TNF levels may be responsible for profound weight loss in AIDS patients whose weight loss cannot be explained by malabsorption or starvation.

It is also possible that elevated cachectin levels may be responsible for the otherwise unexplained serum lipid abnormalities that have been observed in patients with AIDS (20). Such patients may have markedly elevated fasting serum triglycerides; serum cholesterol levels may be slightly elevated, normal, or low. Because TNF is known to suppress lipoprotein lipase and to cause hypertriglyceridemia in experimental animals (21, 22), it is tempting to speculate that cachectin is also responsible for the hypertriglyceridemia observed in patients with AIDS.

It is not clear whether the hypertriglyceridemia in AIDS patients is of clinical significance and needs to be treated, unless the level is high enough to put the patient at risk for pancreatitis. Pancreatitis attributable to hypertriglyceridemia has not been observed in AIDS patients, to our knowledge. It is important, however, to keep the possibility of hypertriglyceridemia in mind in the differential diagnosis of the hyponatremia that may be seen in patients with AIDS for other reasons (for example, adrenal insufficiency or hyporeninemic hypoaldosteronism), since elevated serum triglyceride levels produce pseudohyponatremia.

Treatment of cachexia in patients with AIDS, in addition to the usual measures applied to malnourished patients, may include megestrol acetate, a synthetic progestagen that can stimulate appetite and produce weight gain (23). It has been recently reported that megestrol acetate induced weight gain in 14 patients with AIDS (23). Controlled studies to evaluate the effect of this treatment on patients' weight and the outcome of their disease have not yet been carried out.

Endocrinologic Abnormalities Not Specific for AIDS but Common in AIDS Patients

In addition to the endocrinologic abnormalities that have been described specifically in patients with AIDS, these patients can manifest a variety of endocrinologic and metabolic abnormalities associated with conditions that commonly accompany or are a part of the clinical picture of AIDS. Although discussing these abnormalities in detail is beyond the scope of this review, we feel it is important to keep them in mind while evaluating the AIDS patient.

Thyroid Function. "Sick euthyroid" syndrome (thyroid function tests suggestive of hypothyroidism in the absence of clinical evidence of hypothyroidism) is one such abnormality. Although Dobs and co-workers did not observe this syndrome in their studies of ambulatory patients with AIDS (16), we have frequently encountered it in hospitalized patients with AIDS. The sick euthyroid syndrome can be seen in a variety of nonthyroidal illnesses (24) and is commonly manifested principally by a low serum level of triodothyronine (T3). Serum thyroxine (T4) may also be low, and, in fact, can be used as an index of prognosis: very low T4 levels are associated with poor prognosis (25). Thyrotropin (TSH) levels in patients with sick euthyroid syndrome are usually normal but may rise during recovery from underlying illness, thus mimicking hypothyroidism. The pathogenesis of the findings characteristic of this syndrome is not known, and the consensus today is that no treatment is necessary.

In addition to the sick euthyroid syndrome, patients with AIDS may have a unique pattern of thyroid function test abnormalities recently described by LoPresti with co-workers (26): low reverse T3 (rT3) levels and rising thyroxine-binding globulin (TBG) levels. The pathogenesis and clinical significance of these abnormalities require further study.

Calcium Metabolism. Abnormalities of calcium metabolism constitute another group of metabolic disorders commonly observed in AIDS but not specific to it. Hypocalcemia due to vitamin D deficiency can develop in patients who suffer from diarrhea and malabsorption. It can be distinguished from hypoparathyroidism by the concomitantly low serum phosphorus levels (these are elevated in hypoparathyroidism) and compensatory elevation of serum PTH-levels. Vitamin D deficiency is diagnosed by demonstrating a subnormal serum level of 25-hydroxy vitamin D, the main storage form of the vitamin D. The condition can be treated by supplementation with vitamin D (50,000–100,000 IU orally, twice a week) plus calcium (1,000 mg of elemental calcium daily).

Hypercalcemia may also be present in patients with AIDS. It is related to either accompanying tumors that elaborate humoral hypercalcemic factors or to granulomatous disease. Lymphomas and myobacterial infections are commonly present in patients with AIDS (27–29). The hypercalcemia of malignancy may be due to parathyroid-hormone-like peptides, to various growth factors, or to osteoclast-activating factors (30–33). Granulomatous diseases, including tuberculosis, can produce hypercalcemia through increased conversion of vitamin D to its metabolites in the granulomatous tissue (34, 35). In all these cases the hypercalcemia can be distinguished from that of hyperparathyroidism by the finding of suppressed serum PTH levels. Treatment of the hypercalcemia entails adequate hydration, the administration of diuretics (preferably loop diuretics, such as furosemide), and possibly the use of calcitonin or Mithracin (36).

Drug-Related Endocrinologic Abnormalities Common in AIDS Patients

Several drugs utilized in the treatment of patients with AIDS can produce metabolic aberrations.

Suramin. Suramin, an antiviral agent used in the past, can produce severe, sometimes lethal, adrenal insufficiency (37). The mechanisms of this effect involve inhibition of several cytochrome P-450-regulated steps in glucocorticoid synthesis (38). Because of its capacity to produce adrenal insufficiency, this agent is no longer used for treating patients with AIDS.

Ketoconazole. Ketoconazole, an antifungal agent, is still commonly used in treating complications of AIDS. This drug inhibits steroidogenesis by blocking several essential biosynthetic reactions, and can produce clinically significant adrenal insufficiency (39–41).

Patients with true adrenal insufficiency produced by ketoconazole should be differentiated from patients who have generalized hyperpigmentation that can mimic adrenal insufficiency (42). Such pigmentation may be induced by azidothymidine (AZT), a drug that is commonly used to treat patients with AIDS. The rapid ACTH stimulation test can be used to differentiate these two conditions.

Drugs Affecting Glucose Metabolism. A number of drugs that are commonly used in the treatment of AIDS can affect glucose metabolism. Sulfonamides, such as sulfamethoxazole in the trimethoprim/sulfamethoxazole (Bactrim, Septra) combination, can produce hypoglycemia, particularly in malnourished individuals with depleted liver glycogen stores (43). This hypoglycemic effect is thought to be due to enhanced insulin release from the beta cells of the pancreas. Pentamidine, a beta-cell toxin, can produce hypoglycemia during the initial phase of its action, when insulin is released from the beta cells undergoing destruction. When more than 90% of the beta cells are destroyed, the patient develops permanent hyperglycemia, often accompanied by ketosis (44, 45). This picture is similar to spontaneous type I (insulin-dependent) diabetes, and indeed is a form of diabetes. Such patients require insulin administration.

Other Unusual Drug Effects. You-Hern and Goldman described an unusual complication of treatment with Bactrim (46). They reported on a patient with AIDS and syndrome of inappropriate antidiuretic hormone secretion (SIADH) who developed severe hyponatremia as a result of infusion of large amounts of fluids required for intravenous administration of Bactrim. The authors suggested that the patient's SIADH was due to *Pneumocystis carinii* pneumonia. This unusual cause of hyponatremia should be considered in the differential diagnosis of hyponatremia in AIDS, which also includes adrenal insufficiency, hyporeninemic hypoaldosteronism, and pseudohyponatremia due to hyperlipidemia.

Another unusual metabolic effect that has been attributed to pentamidine is severe hyperkalemia, probably due to acute renal insufficiency (47). Such patients should be differentiated from those with acute adrenal insufficiency or hyporeninemic hypoaldosteronism, which can also present with hyperkalemia (5, 11).

Summary

Various endocrinologic and metabolic abnormalities are seen in patients with AIDS. Some of these abnormalities may be directly related to HIV infection; others may be a manifestation of conditions that accompany HIV infection, such as weight loss, malnutrition, and malabsorption; still others may be induced by the drugs utilized in the treatment of AIDS. Timely diagnosis of these endocrinologic abnormalities permits the institution of effective therapy that can prolong life and improve its quality in patients afflicted with AIDS.

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1. Oberfield SH, Kairam Ram, Bakshi S, Bamji M, Bhushan V, Mayes D, Levine LS. Steroid response to adrenocorticotropin stimulation in children with human immunodeficiency virus infection. J Clin Endocrinol Metab 1990; 70:578–581.
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Commercial IgG Immunoglobulin Preparations Exhibit IgG and IgA Autoantibody Reactivity at Pharmacologic but Not at Physiologic Concentrations

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Abstract

IgG immunoglobulin preparations have been increasingly utilized to treat a variety of diseases. Since disease response to this form of therapy in patients with abnormal autoimmune function is often evaluated through the subsequent investigation of autoantibody levels, it is possible that autoantibody positivities reflect autoantibody reactivity of circulating immunoglobulin preparations and not of the patient's inherent B-cell activity. We therefore investigated three commercially available IgG immunoglobulin preparations separately for IgG, IgM and IgA autoantibody reactivity to six phospholipid antigens, total histone and four histone subfractions, and four polynucleotides. Universally, all three preparations demonstrated considerable IgG antiphospholipid and antihistone reactivity at dilutions of up to 1:10^3 but not antipolynucleotide reactivity. Although no IgM reactivity was detected in any of the preparations, in all three preparations surprising IgA reactivity, especially with antihistone specificity, was detected. No autoantibody reactivity was detected at dilutions compatible with physiologic conditions in vivo. Identical observations were made for lupus anticoagulant reactivity, which was evaluated by activated partial thromboplastin time (APTT) and tissue thromboplastin inhibition (TTI). Since autoantibody reactivities and prolonged APTT assays are observed only at pharmacologic dilution levels, it is unlikely that the administration of IgG immunoglobulin preparation will affect the evaluation of autoantibody levels in patients undergoing such treatment.

IMMUNOGLOBULIN preparations were first utilized for the prevention of anti-D sensitization in Rh-negative pregnant women (1). Since then, the utilization of immunoglobulin preparations has been greatly expanded. Although the exact immunologic action of immunoglobulin preparations is still only poorly understood, it appears that the administration of a concentrated dose of immunoglobulin can affect immune function in a variety of ways. Recent applications have involved enhancement of resistance to infections in immunocompromised hosts (2, 3) and the suppression of a variety of autoimmune diseases (4, 5).

In obstetrical practice, immunoglobulin therapy has recently been suggested for patients with repeated spontaneous miscarriages, believed to be due to abnormal B-lymphocyte function (6, 7). Since these patients, in contrast to patients with

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autoimmune diseases, usually exhibit no clinical autoimmune symptomatology (8), the evaluation of autoantibody abnormalities represents the only option to assess disease response to therapy.

Immunoglobulin preparations can be expected to express idiotypic and anti-idiotypic specificities (9). If they also contain reactivity to specific autoantigens, then the administration of immunoglobulin preparations can result in false positive autoantibody evaluations in patients in whom no other remedy exists to assess disease progress.

We therefore evaluated lupus anticoagulant and autoantibody reactivity of three widely used, commercially available immunoglobulin preparations at different concentrations. Although autoantibody reactivities were detected at pharmacologic concentrations in all preparations, this study also suggests that no such reactivity exists at physiologic levels reached in vivo.

Materials and Methods

The three intravenous human immunoglobulin preparations investigated were Sandoglobulin (Sandoz Pharmaceuticals Corporation, East Hanover, NJ), Gamimune N (Miles Inc., Cutter Biological, Elkhart, IN), for intravenous use, and Gammar (Armour Pharmaceutical Company, Kankakee, IL) for intramuscular use.

All three investigated preparations are reported to primarily contain monomeric (7S) IgG immunoglobulins in distributions of IgG subclasses similar to those in normal human serum. All preparations also contain traces of dimeric and polymeric IgG, as well as small quantities of IgA and IgM immunoglobulins. They are produced by cold ethanol fractionation of large pools of human plasma and are nonreactive for hepatitis B surface antigen. The product package inserts indicate that the products contain a broad spectrum of antibody specificities against bacterial and viral antigens.

The half-life of the intravenous and intramuscular preparations is reported by the manufacturers to be approximately 3 weeks. Intravenous preparations reach an equilibrium of 50%:50% between intravascular and extravascular compartments after approximately 6 days. After intramuscular injection, IgG concentrations reach an intravascular maximum of 40% after 2–5 days.

Lupus Anticoagulant Determination. The presence of lupus anticoagulant in immunoglobulin preparations was demonstrated with the tissue thromboplastin inhibition (TTI) test and the activated partial thromboplastin time (APTT). Normal human plasma samples were utilized to dilute immunoglobulin preparations in a range between 1:1 and 1:10^5. A TTI above 1.3 in the presence of a prolonged APTT, without correction by addition of normal plasma at a ratio of 1:1, was considered indicative of the presence of lupus anticoagulant activity.

The APTT was performed according to the method of Proctor and Rappaport (10), using a partial thromboplastin prepared from rabbit brain by the method of Babson and Babson (11). The partial thromboplastin was diluted to give a normal APTT of 38–39 s and then stabilized with 0.03 M Hepes buffer and adjusted to pH 7.0 with 1.0 *N* NaOH. For use, 3 mL of partial thromboplastin was mixed with purified water; 0.1 mL of patient plasma was then added to 0.1 mL of this mixture and incubated for 5 min at 37°C. Immediately after incubation, 0.1 mL of 0.025 M $CaCl_2$, prewarmed to 37°C, was added and the time to clot formation noted. Clotting times were measured in duplicate on the Bio-Data Coagulation Analyzer (Bio-Data). The normal range for the APTT in our laboratory was determined to be below 40 seconds (mean ± 2 SD).

The TTI was performed according to the method of Mannucci et al (12) using a commercially available tissue thromboplastin (Simplastin, General Diagnostics, Division of Warner-Lambert Company, Morris Plains, NJ). The tissue thromboplastin was diluted 1:500 in 0.9% saline and 0.1 mL mixed with 0.1 mL of patient plasma was added and incubated for 3 min at 37°C. Then 0.1 mL of 0.025 M $CaCl_2$, prewarmed to 37°C, was added and the time to clot formation was noted. Each dilution of tissue thromboplastin was tested separately with a normal control plasma and the patient's plasma within 30 min of preparation. Clotting times were measured in duplicate using a Bio-Data Coagulation Analyzer (Bio-Data). A ratio of the patient's clotting time to the control clotting time was then calculated. A value of 1.30 or greater was considered abnormal. A value of 1.20–1.29 was considered borderline positive.

Autoantibody Assays. Autoantibody investigations of immunoglobulin preparations were performed in increasing dilution of immunoglobulin preparations with fetal calf serum within a range of 1:1–1:10^5. Antibodies to six phospholipid antigens (cardiolipin, phosphatidylserine, phosphatidic acid, phosphatidylethanolamine, phosphatidylglycerol, phosphatidyl inositol), five histones and histone subfractions (H1, H2A, H2B, H3, and H4), and four polynucleotides (ssDNA, dsDNA, Poly (I), and Poly [dT]) were evaluated separately for IgG, IgM, and IgA isotypes.

The presence of autoantibody reactivity was evaluated following the method of Loizou et al (13) as previously described in detail (14). In brief, antiphospholipid antibodies were quantitated with the following method: The purified phospholipids cardiolipin, phosphatidylserine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidyl-inositol, and phosphatidic acid (Avanti, Birmingham, AL) were left on plates (Maxisorp, Nunc, Denmark) (100 μg/mL) until all organic saline solvents were dried (4°C under vacuum).

Plates were incubated with phosphate-buffered saline solution and fetal calf serum (10%) to block nonspecific binding. After washing with 0.05% phosphate-buffered saline solution and Tween, duplicate serum samples, diluted 1:150, were incubated for 12 hr at 4°C. After further washing, affinity-purified, alkaline phosphatase–conjugated goat antihuman IgG, IgM, and IgA (1:1000, Sigma Chemicals, St. Louis, MO) in phosphate-buffered solution and fetal calf serum (10%) were added for 3 hr. The plates were then washed with 0.05% phosphate-buffered saline solution and Tween and 1 mg/mL of *p*-nitrophenyl disodium phosphate (Sigma Chemicals) in 1 mol/L diethanolamine. An aliquote of 0.5 mmol/L magnesium chloride at pH 10.4 was added as substrate. The reaction was allowed to proceed for 25 min at 50°C in the dark. Optical density was recorded with a Bio-Tek multiscanner EL-309 (Bio-Tek Instruments, Highland Park, VA). Results are expressed in optical density units × 10Y3H at 405 μm. Control sera with known elevated IgG and IgM levels (donated by Dr. Nigel Harris, formerly of St. Thomas Hospital, London, England), eight samples of normal control sera (representing the range of 100 normal controls), and a blank well with no serum were assayed in parallel in each plate.

Antihistone and antipolynucleotide antibodies were assayed as previously described (14). As with antiphospholipid antibodies, 10 previously screened control sera, a known positive control serum, and a blank sample were put in parallel in each plate. All samples were run in duplicate. Intrassay and interassay variability was 2%–4.5% and 4%–7.5%, respectively, for all autoantibodies. Autoantibody positivity was arbitrarily defined at the same level as in the departmental clinical autoantibody laboratory. It is based on the 99% confidence limit of 400 control samples, obtained from apparently healthy blood donors.

Results

All TTI results of investigated immunoglobulin preparations were uniformly normal at levels below 1.3. APTT values of three investigated patient samples uniformly increased at highest concentrations of immunoglobulin (1:1), but returned to normal values at concentrations of 1:10 and below (Fig. 1).

Sandoglobulin revealed antiphospholipid antibody reactivity to all six investigated antiphospholipid antibodies among IgG and IgA isotypes. Especially among IgG isotypes, this reactivity was primarily detected at high concentrations of the preparation. Similar observations were made for antihistone antibodies. No IgM activity was noted for either autoantibody grouping, nor was any reactivity detected against polynucleotide antigens (Fig. 2).

Gamimune demonstrated an almost identical pattern of autoantibody reactivity as Sandoglobulin (Fig. 3). Once again, most reactivity appeared at high product concentrations and was restricted to IgG and IgA isotypes of antiphospholipid and antihistone reactivity.

Gammar, the intramuscular preparation, also demonstrated similar autoantibody reactivity, though it was somewhat more pronounced, especially among antihistones (Fig. 4). Otherwise, reactivity was also restricted to IgG and IgA isotypes of antiphospholipids and antihistones.

Discussion

Immunoglobulin preparations have achieved wide utilization in various areas of medical practice. Their use is no longer restricted to the initial obstetrical application in Rh-negative mothers (1) but has expanded to a variety of immunodeficiencies, infectious diseases, and autoimmune conditions (2–6). The apparently successful utilization of immunoglobulin preparations in autoimmune diseases has led to the proposal to utilize this treatment approach in patients with repeated abortions, which etiologically have been linked to abnormal B-cell function (8). At this point such use is still mostly a theoretical concept, but some investigators have already reported anecdotal experience (6, 7).

In contrast to patients with defined autoimmune diseases, women whose repeated miscarriages are believed to be due to abnormal B-cell function are clinically asymptomatic (8). The diagnosis of pregnancy wastage due to an assumed B-cell defect is therefore based almost solely on such laboratory tests as lupus anticoagulant (8, 15) or autoantibody tests (16). Moreover, treatment success can only be monitored by following these laboratory tests in a longitudinal fashion since clinical symptomatology does not exist.

The total dependence on laboratory tests in diagnosis and treatment of these patients raises the question whether the administration of immunoglobulin preparations can affect autoantibody evaluations in these patients. Autoantibody reactivity can be expected to be present in those immunoglobulin preparations since, at least in the IgG fraction, they represent all IgG classes in distributions similar to those found in serum (17). Moreover, the manufacturers also acknowledge the presence of traces of IgM and IgA.

Lupus anticoagulant is believed to represent a compendium of immunoglobulins, though its specific antibody correlation has remained undetermined (18). Although a correlation with antiphospholipid antibodies appears to exist, it is not as close as reported by some investigators and extends to such other autoantibody groupings as antihistones and antipolynucleotides (19). The detection of APTT activity (in high immunoglobulin concentrations) in the preparations evaluated here therefore comes as no surprise. Why TTI activity was not detected remains, however, to be explained.

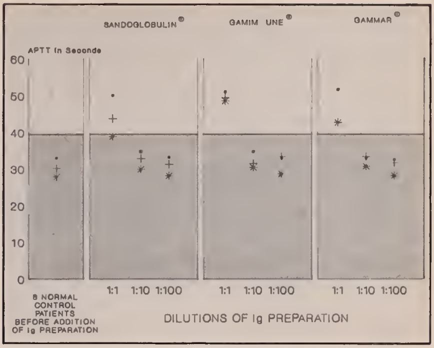


Fig. 1. APTT levels at different concentrations of immunoglobulin preparations. No TTI positivity was detected in any of the investigated samples.

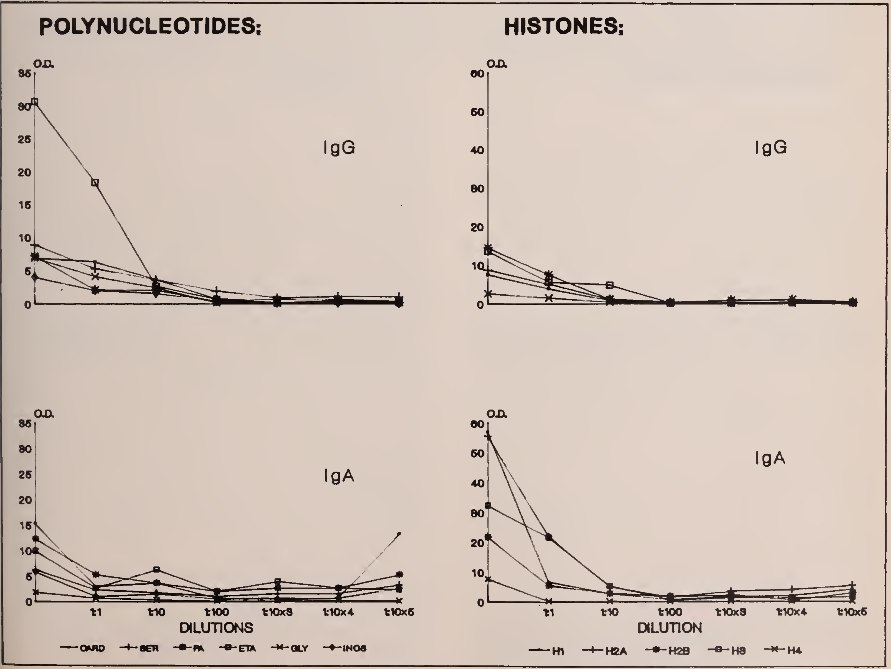


Fig. 2. Autoantibody reactivity detected in Sandoglobulin. Only clinically considered positive reactivities are shown.

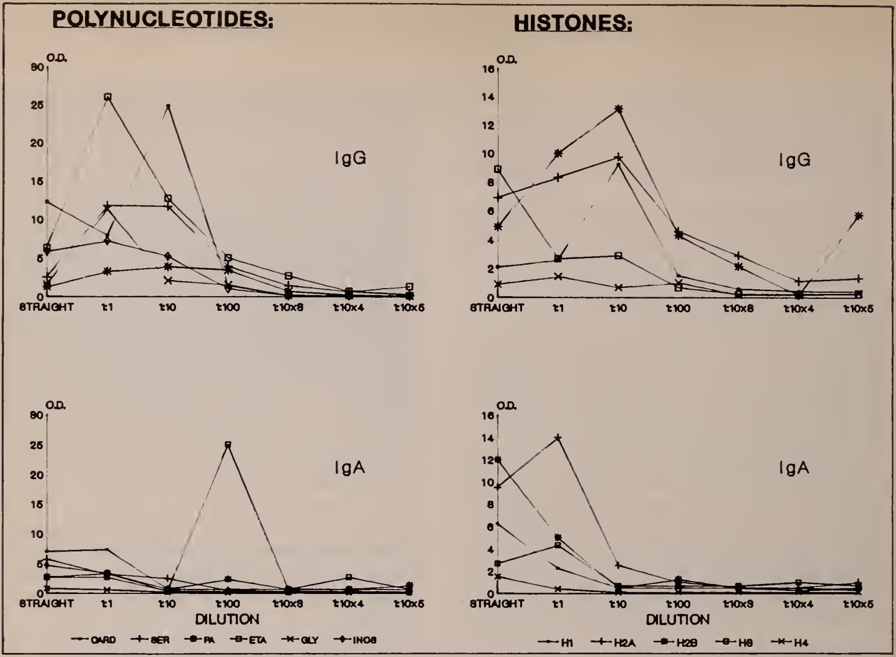
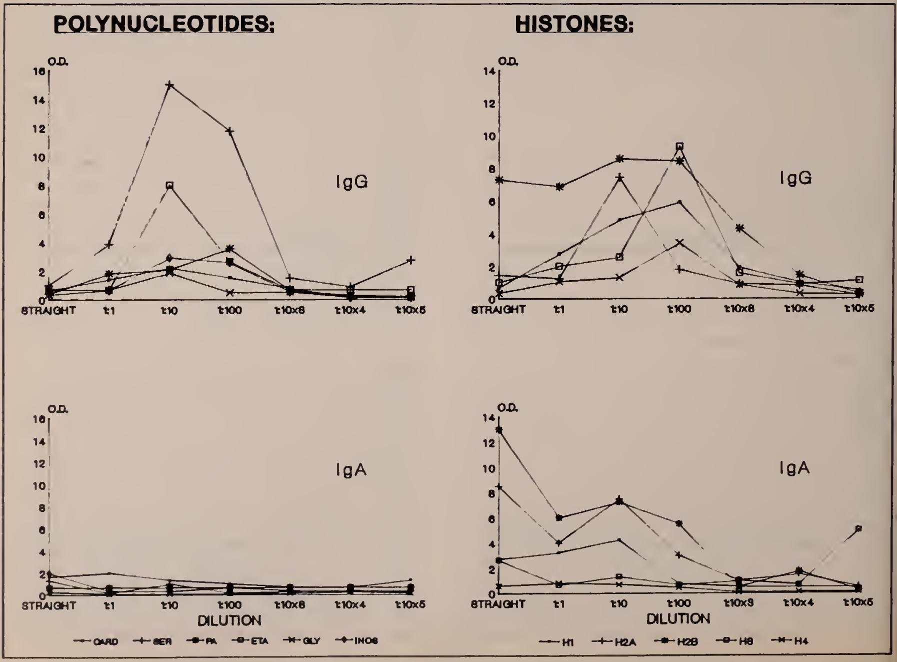


Fig. 3. Above Autoantibody reactivity detected in Gamimune. Only clinically considered positive reactivities are shown.
Fig. 4. Below Autoantibody reactivity detected in Gammar. Only clinically considered positive reactivities are shown.



Autoantibody reactivity was detectable (in correlation with APTT activity) at high immunoglobulin concentrations. Quite surprisingly, however, this autoantibody activity was restricted to antiphospholipids and antihistones and appeared almost evenly among IgG and IgA isotypes only.

The appearance of autoantibody activity among IgG isotypes is expected, since at least 96% of all immunoglobulin preparations are IgG immunoglobulins. The prominent appearance of IgA reactivity comes, however, as a surprise and cannot be explained by the trace presence of IgA in the commercial immunoglobulin preparations. This observation raises the intriguing question whether the detected IgA activity represents actual IgA autoantibodies, or cross-reactivities, or the false positive detection of antibodies. Cowchock et al. recently reported that high total IgM concentrations can result in false positive autoantibody evaluations in ELISA tests (20). No IgM activity at all was, however, detected in any of the immunoglobulin preparations.

APTT as well as autoantibody activity was principally detected only at high immunoglobulin concentrations. At lower concentrations this activity disappeared. Two explanations are possible for this finding: First, Cowchock's observation that high total IgM concentrations result in the false positive detection of autoantibody activity (20) could also be applicable to IgG reactivity. This explanation is unlikely since most of the IgG in immunoglobulin preparations is monomeric 7S (21) and Cowchock associated the false positive detection of autoantibodies with the polymeric nature of IgM (20). Small amounts of polymeric IgG and traces of IgM are, however, present in immunoglobulin preparations. A second possible explanation can be based on the existence of idiotype-antiidiotype reactions within immunoglobulin preparations that are dose dependent (9).

Intravenous administration of immunoglobulins has been associated with normalization of both lupus anticoagulant and autoantibody levels in vivo (6, 7) but does not necessarily correlate with results obtained in vitro (6). This discrepancy between in vivo and in vitro results is only part of the remaining enigma surrounding the mode of action of immunoglobulin preparations on the immune system. This study was not designed to address the question of how immunoglobulin preparations exert their beneficial therapeutic effect. It was conceived to rule out iatrogenically induced false positive autoantibody results in immunoglobulin-treated patients. From this report it appears that such a situation is unlikely to occur.

Immediately after intravenous injection, 100% of the immunoglobulin dose is in the recipient's circulation (21). However, even at such an early stage it appears that the dilutional effect of the circulatory distribution will result in immunoglobulin concentrations which, based on the dilution experiments reported here, would not result in either lupus anticoagulant or autoantibody-positive reactivity. Although such a possibility cannot be completely ruled out, a timely delay in performance of venipuncture after administration of an immunoglobulin preparation should further decrease the likelihood of this unlikely occurrence.

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The Formulary

Bernard Mehl, D.P.S., editor

Recombinant Hepatitis B Vaccine

RECOMBINANT hepatitis B vaccine (Engerix-B) is supplied in a 20 mcg/mL single vial. Recommended doses for this product are as follows:

neonates & children to 10 years	10 mcg (0.5 mL)
other children and adults	20 mcg (1.0 mL)
adults, on hemodialysis or immunocompromised	40 mcg (2.0 mL)

Engerix-B can be administered according to two dosing schedules. The standard schedule is to administer 20 mcg initially, followed by 20 mcg at 1 and 6 months after the initial dose. Alternatively, Engerix-B can be administered on a 0, 1, 2, and 12-month schedule. The accelerated dosing schedule is for those patients who need rapid development of antibody levels. Populations that may benefit from this dosing schedule include those recently exposed to the virus, especially neonates born to infected mothers and certain travellers to high-risk areas. This alternate dosing regimen for Engerix-B may provide for more rapid development of antibody levels than does the standard schedule.

When Engerix-B is used to treat adult hemodialysis patients, 40 mcg doses are used; the dose should be divided and given at two separate sites.

Student Corner

Tailgut Cyst (Retrorectal Cyst Hamartoma):

Case Report and Review

DANIEL J. PYO, M.D.

TUMORS originating in the retrorectal space are uncommon and are frequently unrecognized, misdiagnosed, and mistreated. Tailgut cysts are rare congenital lesions that appear initially as a presacral mass, found in infancy or persisting undetected into adulthood. They are believed to arise from a vestige of the embryonic hindgut, and are characterized by multiple cysts lined with a gastrointestinal type of epithelium. They have been described in the literature by various terms: cyst of postanal intestine, retrorectal cyst-hamartoma, tailgut vestiges, myoepithelial hamartoma of the rectum, tailgut cyst, developmental cyst, and rectal cyst (1–4).

A representative case is presented, along with a review of the literature. The anatomy and postulated embryology of the retrorectal space are described. The differential diagnosis and management of retrorectal tumors is also discussed briefly. Finally, some controversial issues surrounding these tumors are mentioned.

Case Report

A 38-year-old white woman developed sudden onset of crampy suprapubic abdominal pain, fevers to 103°F, and headache. One week prior to admission, she developed abdominal pain, fevers, headache, malaise, myalgias, chills, loss of appetite, and generalized weakness. She described an episode of pelvic pain, dysuria, and a painful, mucoid bowel movement. She reported no nausea or vomiting, hematemesis, melena, jaundice, diarrhea, genitourinary, or gynecologic symptoms, anorectal pain, discharge, fullness, or bleeding. A private physician noted moderate suprapubic abdominal pain, with rebound tenderness. Studies to detect an obstruction, chest x-ray, and abdominal and pelvic sonogram were negative except for gallstones. On the day of admission she developed a temperature of 101°F and increasing lower abdominal rebound tenderness, and was admitted to the surgical service.

Her medical history was significant for mitral valve prolapse diagnosed in 1986, fibrocystic breast disease, chronic constipation and hemorrhoids. Rectal polypectomy was performed in 1986 at another hospital; the histologic study results are unknown. Her father had a myocardial infarction, and a brother had ulcerative colitis. She had had herpes infection, and she denied the practice of anal intercourse.

Examination revealed a well-developed, well-nourished young woman in moderate distress. The abdomen was nondistended, with diminished bowel sounds, and was tender to both superficial and deep palpation, with rebound tenderness in both lower quadrants. On digital rectal examination, a smooth, tender, round mass, approximately 2 × 2 cm, was palpable on the posterolateral rectal wall, 4 to 5 cm from the anal verge. It was firm and fixed in relation to the coccyx and perirectal tissues. There was no edema, ulceration, or other irregularity of the rectal mucosa overlying the lesion. There were no other significant physical findings.

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Laboratory studies included normal results on urinalysis and electrolytes. The white blood cell count was 15,100, with an elevated eosinophil count of 16%. The hematocrit was 35.2% and the hemoglobin 11.9 g/100 mL. Initial sedimentation rate was 100. There was an elevated alkaline phosphatase of 260, and an elevated ALT of 127. The chest x-ray and electrocardiogram were normal. Indium scan showed no distinct areas of inflammation; a barium enema study revealed an extrinsic mass effect on the posteroinferior sigmoid colon. A CT scan of the lower abdomen and pelvis showed a large retroperitoneal soft tissue mass posterior to the rectum. The preoperative diagnosis was a soft tissue tumor posterior to the rectum.

At surgery, the patient underwent general anesthesia, and a transabdominal approach was attempted. The mass was identified as a large 8 × 10 cm, yellow-green, gelatinous structure adherent to the posterior portion of the superior two-thirds of the rectum and coccyx. Because the mass could not be dissected freely from the rectum, a low anterior resection was performed. The margins were grossly clear of the mass and were reanastamosed using the CEEA stapler. Frozen-section examination revealed no evidence of malignancy.

The patient had an uneventful postoperative course and was discharged on the 7th day after surgery. A preliminary pathology report indicated that the mass did not contain tumor tissue, but that inflammatory tissue was present. The final diagnosis was inconclusive, indicating abundant inflammatory tissue and no evidence of malignancy.

Discussion

The retrorectal region is a potential space developing only when the rectum is displaced anteriorly by a mass. It is bounded anteriorly by the rectum and posteriorly by the sacrum and coccyx. It extends proximally to a point where the peritoneum is reflected onto the rectum, at about the junction of the second and third sacral segments. Distally the levators ani and coccygeal muscles form the floor, while laterally the boundaries are formed by the peritoneal reflection assisted by the lateral rectal stalks, the iliac vessels, and the ureter. Within this area are the branches of the sacral plexus, sympathetic plexus of nerves, and the middle sacral, iliolumbar, and middle hemorrhoidal vessels and lymphatics (2, 3, 5).

Retrorectal cysts are thought to be of developmental origin, although their precise embryologic basis is unknown. Some investigators have suggested that they originate from persistent remnants of the embryonic postanal gut, or tailgut (6, 7). In the human embryo, the postanal gut is present during the 3.5 to 8.0 mm stage of development, at a time when the embryo possesses a true tail (1). The anus is formed cephalad to the tail. Because the primitive gut extends into the tail beyond the point at which the anus develops, it is called the tailgut or postanal gut. Normally, the postanal gut, a tubular structure lined with two to four layers of stratified cuboidal epithelium, fills with epithelial debris and mucus before completely disappearing. Within this location, many organ systems, including the primitive gut, the urogenital tract, early skeletal systems, vascular and lymphatic channels, and the neural tube, develop. Anomalies originate from arrested development or failure of regression in any of these organ systems (5–7).

In order to identify a tumor as of tailgut origin, it must be within the retrorectal space, have an intestinal type of epithelial lining, and have no definite muscular or serous coat (1, 6). Possible origins for such cysts include the proctodeal membrane, coccygeal vestiges, the neurenteric canal, the postanal gut, and ectodermal inclusions formed during faulty coalescence of cutaneous surfaces in embryonic life (8, 9).

Tailgut cysts should be distinguished from other lesions occurring in the retrorectal space and in the perianal area. These include teratomas, dermoid cysts, duplication cysts of the rectum, anal gland cysts, and anal gland carcinomas. The classification of these masses in the retrorectal region is dependent on the type of epithelium present. Dermoid cysts are lined by stratified squamous epithelium and contain dermal appendages in the wall closely associated with or actually communicating with the cyst lining (5, 10). They are thought to arise through faulty inclusion of ectoderm when the embryo coalesces (5, 11, 12). Enteric cysts or duplications are lined by squamous or glandular epithelium of intestinal type with characteristic villi and crypts. In addition they contain one or more layers of well-developed smooth muscle, a myenteric plexus, and a serosa (7, 11). Teratomas are characterized by the presence of derivatives of the three germ layers. They may be lined with squamous, cuboidal, ciliated, or cylindric epithelium. They are almost always seen in infants and the newborn, rarely in adults. Anal gland cysts are usually located in close relationship to the anal sphincter, a feature which readily differentiates them from tailgut cysts, although they commonly contain similar epithelial elements. Anal gland carcinomas may occur in the submucosa of the anus or in perirectal tissue, or they may be associated with anal fistulas. They are characterized by the presence of large amounts of mucus, resembling the tailgut cysts grossly. However, microscopic examination readily demonstrates the malignant features of this lesion.

Tailgut cysts contain a variety of epithelia but always some elements of intestinal epithelium (7, 10). The lining is usually flattened and does not have a complex structure with villi and crypts, as seen in normal bowel.

Grossly, tailgut cysts are soft, multiloculated masses, usually adherent to the sacrum or rectum. If uninfected, they are usually thin walled, have a glistening lining, and are filled with abundant mucoid material. Infection or inflammation may cause fibrosis of the cyst wall and breakdown of the cyst lining. Such changes are seen in about half of all cases (3). The entire mass is usually several centimeters in diameter.

Middeldorpf, in 1885, described a congenital sacrococcygeal tumor that originated from remnants of the postanal intestine. He reported the case of a one-year-old girl with a presacral tumor composed of a loop of bowel similar to the colon, embedded in adipose tissue, and lacking a serosa. Subsequent authors referred to any type of congenital cystic presacral tumor, most frequently teratomas, as Middeldorpf tumors, although his description appears to refer to a rectal duplication (1, 7, 12). In 1928, Peyron investigated the embryologic tailgut and decided that a tumor derived from the tailgut if it was an anterior sacrococcygeal or retrorectal cyst with an epithelial lining of intestinal type without a definite muscular or serous coat. The term "tailgut vestige" was introduced in 1938 by Gius and Stout, who described the embryology of the anorectal canal and reported two cases of retrorectal cyst-hamartomas (5, 12). In 1961, Edwards introduced the term "retrorectal cyst-hamartoma" (13). Most recently, Hjermstad proposed the term "tailgut cyst" because it is "descriptive, unambiguous, and easy to say" (7).

Reports of initial symptoms vary from anorectal pain, dysuria, diarrhea, history of recurring perianal fistulas or abscesses, to no symptoms at all. Hjermstad, in his most recent review of tailgut cyst cases reported in the literature since 1931, reports (7) that the majority of patients who were symptomatic (50%) complained initially of pain either in the rectal area or the lower back. Others complained of rectal fullness, painless rectal bleeding, urinary frequency, and a change in the caliber of the stool. Theuerkauf reported that uninfected cysts may lie dormant for years, and that patients are usually asymptomatic and thus are unaware of the cysts (4). Rarely, unusually large cysts may displace the rectum and cause constipation, diarrhea, tenesmus, or low-back ache. They may also cause numbness and discomfort in sitting, and may be mistaken for a pelvic tumor, an ovarian cyst, or an intraligamentous fibroma.

There is a significant female predominance in the cases of tailgut cysts reported, with an approximate 3-to-1 female-to-male ratio. The average age of initial symptoms for the women was in the middle to late thirties. The age distribution for the men showed greater diversity without a significant peak.

The most common problems occur when the cysts become infected. Trauma and infection via the lymphatics or a congenital sinus have been suggested as possible causes. Usually when this occurs, symptoms of pain, fever, and chills develop. The cyst may rupture into the perianal skin, usually between the coccyx and the anus, and the resulting sinus may discharge pus or bloody fluid. The cyst may also rupture into the rectum, or the infection may travel upward. If the cyst does not rupture, it may remain as a fluctuant or nonfluctuant enlarging perirectal mass.

Carcinoma developing in a tailgut cyst is rare, but has been reported in the literature (12, 14, 15). Marco describes such a case, of an adenocarcinoma complicating a tailgut cyst (12). Cases have also been reported by Ballantine, Crowley and Page, Spencer and Jackman, and Malafosse (11, 12, 14). In the cases reported by Ballantine and Malafosse, the patients developed local recurrences, lung metastases, and inguinal node metastases, and all patients were dead with evidence of disease 8 months after removal of the cysts (15). The case reported by Crowley included perianal recurrence, documented by biopsy, 12 months after removal of the tumor (14).

Careful digital rectal examination should be the first step in the diagnosis of tailgut cysts, followed by proctosigmoidoscopy. Roentgenographic studies should include anteroposterior and lateral projections of the sacrum and coccyx. A barium enema study can be of value in assessing the size of a tumor, but several researchers judge that it merely confirms the presence of an extrinsic retrorectal mass (3, 11, 16). Ultrasonographic examination and computerized axial tomography are helpful in demonstrating the complex cystic nature of these tumors.

Complete surgical excision is the treatment of choice for all retrorectal tumors. Although small benign tumors, such as the tailgut cyst, can be removed transrectally or perirectally, an abdominal approach is recommended for lesions larger than 5 cm, regardless of the histologic type. Some authors believe that incisional biopsy is not usually indicated because it provides only limited material for diagnosis, and subsequent follow-up excision always should be performed anyway (16). Hjermstad advocates the posterior approach because it offers the best chance of identifying and removing the lesion in most patients (7). He discourages transanal resection because limited visualization of the retrorectal space carries the risk of leaving other cysts behind. Other approaches suggested include a dorsal approach through a paracoccygeal incision, a Kraske-type longitudinal incision with excision of the coccyx, a transverse incision over the tumor between the coccyx and the anus, or a combined abdominoperineal approach.

Whatever approach is used, complete excision is of utmost importance, and an anterior resection or abdominoperineal resection should be performed if needed. All tumors in this area should be surgically removed, first, to relieve any symptoms that may be present, since the tumors may grow to a large size, and produce recurrent perianal fistulas; second, to reduce the potential for infection in this closed space, which makes removal much more difficult and dangerous; and third, to rule out the presence of malignancy.

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Abstracts

The abstracts presented here, all by principal investigators in the Department of Medicine of the Mount Sinai School of Medicine (which includes the affiliates Beth Israel Medical Center, the Bronx Veterans Administration Medical Center, and Elmhurst Hospital Center), were exhibited as posters in the Department of Medicine Eighth Annual Research Day, September 17, 1990. Only those abstracts by principal investigators who have consented to publication in the Journal *are included.*

Abstracts by students, fellows, and house staff working in the Department of Medicine are presented as Part 2. Five of these abstracts received Eighth Annual Department of Medicine Research Awards and were presented orally at a Special Grand Rounds on September 18; each of those five abstracts is identified by a bullet.—Robert Safirstein

Research Day in Medicine 1990

Part 1

Alcohol Research and Treatment Center

Effect of Liver Disease on Red Blood Cell Acetaldehyde in Alcoholics and Non-alcoholics. R Uppal, A Rosman, R Hernandez, E Baraona and CS Lieber, Alcohol Research & Treatment Center, Bronx VA Medical Center & Mount Sinai School of Medicine (CUNY), Bronx, NY 10468.

We recently reported that experimentally induced liver injury in rats increases the levels of acetaldehyde (Ac) both from endogenous sources and from exogenous ethanol. Since Ac is a potential hepatotoxin, we investigated whether similar alterations are found in patients with non-alcoholic liver disease (NALD) or in patients with alcoholic liver disease after prolonged abstinence. Red blood cell (RBC) Ac was measured in 18 healthy volunteers, 10 patients with alcoholic cirrhosis abstinent for at least 6 months, and 28 patients with a variety of NALD's. The mean RBC Ac in patients with NALD (5.3 ± 0.6 μM) and in abstinent alcoholic cirrhotics (3.7 ± 0.5) were significantly greater than in controls (1.56 ± 0.22) ($p < 0.01$). To investigate whether the Ac response to ethanol consumption was affected by the presence of liver disease, we measured RBC ethanol and Ac in 16 actively drinking alcoholics; 8 with severe liver disease (cirrhosis and/or hepatitis) and 8 with steatosis without fibrosis (documented by recent liver biopsy). Whereas the levels of ethanol were comparable in both groups (21.32 ± 4.8 vs 29.81 ± 5.5, NS), RBC Ac levels were significantly higher in the alcoholics with severe liver disease as compared to patients with steatosis (27.01 ± 5.02 vs 11.56 ± 1.47, $p < 0.05$). Furthermore, at 2–3 weeks after withdrawal, the RBC Ac levels remained elevated in both groups, but were significantly greater in those with severe liver disease (6.65 ± 0.76 vs 2.97 ± 0.24, $p < 0.01$).

In conclusion liver injury promotes accumulation of acetaldehyde from ethanol as well as from physiologic sources and this may further exacerbate the liver damage, setting up a vicious cycle.

Aspirin Increases Blood Alcohol Concentrations after Ingestion of Ethanol. Risto Roine, R Thomas Gentry, Rolando Hernández-Muñoz, Enrique Baraona, Charles S Lieber, Alcohol Research and Treatment Center, VAMC, Bronx, NY & Mount Sinai School of Medicine, NY, 10468.

Some drugs have been shown to decrease gastric alcohol dehydrogenase (ADH) activity in vitro leading to decreased gastric "first pass" metabolism of alcohol and consequently to increased blood alcohol concentrations (BAC) after ingestion of ethanol. The aim of this study was to determine if the widely used drug, aspirin, has such effects.

At concentrations likely to occur in the lumen of the stomach (up to 10 mM = 1.8 g/l), aspirin clearly decreased rat gastric ADH activity. At 5 and 10 mM concentrations, ADH activity was reduced to 55 and 41% of baseline ($p < 0.01$). This inhibition was non-competitive with a Ki of 8 mM. In five healthy male human volunteers, aspirin (1 g perorally together with a standard breakfast 60 min before ingestion of 0.3 g/kg b.w. ethanol) increased the area under the BAC curve by 25%, from 8.79 ± 1.16 to 11.01 ± 1.27 mM*hr (mean ± SEM, $p < 0.02$). At the same time mean peak BAC increased from 5.53 ± 0.63 to 7.30 ± 0.41 mM ($p < 0.05$). To rule out a possible effect of aspirin on hepatic oxidation of alcohol, we studied eight male rats given aspirin intragastrically (200 mg/kg) 110 min prior to intravenous ethanol (0.25 g/kg b.w.). No significant effect on BAC was found with this dose of aspirin reported to produce in rats a blood salicylate concentration in a range considered to be therapeutic for humans, nor was rat liver ADH activity affected by aspirin. Possible effects of aspirin on gastric emptying remain to be studied.

In conclusion: 1) At a therapeutic dosage, aspirin significantly increases blood alcohol concentrations after ingestion of ethanol and thus may potentiate its harmful effects; 2) this increase results, at least in part, from decreased gastric "first pass" metabolism of alcohol subsequent to decreased gastric ADH activity.

Inhibition of Cathepsin B Reduces the Severity of Experimental Pancreatitis in the Rat. MA Korsten JW Dlugosz, J Saeli and CS Lieber, Alcohol Research Center, Bronx VA Medical Center, Bronx, NY and Mount Sinai School of Medicine, NY, NY.

It has been proposed that intracellular activation of trypsinogen by cathepsin B is an initial step in the development of acute pancreatitis. To test this hypothesis, we employed a specific inhibitor of cathepsin B activity, trans-epoxysuccinyl-L-leucylamido-butane (E-64) in two rat models of acute pancreatitis: caerulein-induced (predominantly edematous) and sodium taurocholate-induced (mostly necrohemorrhagic).

Within 1 hour of intravenous administration of E-64 (1 mg/100 gm B.W.), pancreatic cathepsin B in the 150g supernatant and in the lysosomal pancreatic weight nor the serum α-amylase. Pancreatitis was induced in overnight fasted Sprague Dawley rats by intravenous infusion of supramaximal doses of caerulein (5 μg/hr/kg) or intraductal injection of 5% sodium taurocholate (NaTC) (n-12 in each group). One-half the animals in each group received an infusion of E-64 one hour prior to induction of pancreatitis. Rats were sacrificed after 3.5 hours of caerulein infusion and 3 hrs after NaTC injection. Free active trypsin (without activation with enterokinase) and total potential trypsin (after activation by enterokinase for ½ hr. at 37°C) were estimated in the postnuclear pancreatic supernatant. Caerulein increased the serum α-amylase (from 1286 ± 113 to 8209 ± 1044 U/L, $p < 0.001$), a rise that was partly attenuated by pretreatment with E-64 (5317 ± 476, $p < 0.01$). Similarly in NaTC-induced pancreatitis, the increase in serum α-amylase was significantly less in rats pretreated with E-64 (5674 ± 551 vs. 9872 ± 1111, $p < 0.001$). Pancreatic levels of free active trypsin were also significantly lower in E-64 pretreated rats with NaTC pancreatitis than in controls (0.28 ± 0.03 vs 0.51 ± 0.08 μg/mg protein/min, $p < 0.001$). The ratio of total enterokinase-activated trypsin to free active trypsin was significantly higher in rats pretreated with E-64 (21.7 vs 12.3 respectively, $p < 0.05$), suggesting limited trypsinogen consumption in NaTC pancreatitis. However, the increase in pancreatic weight caused by either caerulein or NaTC was not modified by pretreatment with E-64.

In summary, inhibition of cathepsin B by E-64 decreases parameters that reflect the extent of pancreatic injury. These results indicate that cathepsin B is involved in the pathogenesis of both edematous and hemorrhagic forms of pancreatitis and that its inhibition may reduce the severity of acute pancreatic injury.

Molecular Regulation of Hepatic Ethanol-Inducible P450IIE1 Protein and Encoding mRNA: Differences between Species. Y Ito, S Kubota-Kashio, M Tsutsumi, JM Lasker, and CS Lieber, Section on Liver Disease and Nutrition, Alcohol Research Center, Mount Sinai School of Medicine and Bronx Veterans Administration Medical Center, Bronx, NY.

P450IIE1 (IIE1), an ethanol-inducible cytochrome P450 enzyme, plays an important role in the enhanced susceptibility of alcoholics to environmental chemical insults. Agents such as acetaminophen, benzene, carbon tetrachloride, nitrosamines and ethanol itself are all extensively bioactivated by IIE1 to cytotoxic and/or carcinogenic metabolites. The mechanism of IIE1 induction by ethanol and other small organic molecules (e.g., acetone) remains controversial at present, with proposals including substrate-mediated enzyme stabilization in rats (Song et al., JBC 264:3568, 1989) and enhanced enzyme synthesis from increased translatable IIE1 mRNA in hamsters (Kubota et al., BBRC 250:304, 1988).

To test these hypotheses, we first examined hepatic enzyme levels (on blots of polysomal RNA with IIE1 cDNA) in naive or ethanol-treated hamsters and rats (10% ethanol in H_2O for 10 days); the latter animals were also pair-fed liquid diets containing either ethanol (36% of energy) or isocaloric carbohydrate (controls). A two-fold increase in liver IIE1 mRNA content, paralleling that of microsomal IIE1 immunoreactive protein and p-nitrophenol hydroxylation (a IIE1-catalyzed reaction), was observed in ethanol-treated hamsters. In contrast, rats given ethanol had either unaltered or reduced hepatic IIE1 mRNA, despite large increases (3.5-fold for ethanol in H_2O, 5.6-fold in liquid diets) in microsomal IIE1 enzyme content and activity. To explain the ethanol-mediated IIE1 protein induction in rats without an accompanying increase in encoding mRNA, we then determined steady-state IIE1 enzyme turnover rates in vivo with $[^{35}S]$methionine plus $[^{3}H]$aminolevulinate to radiolabel IIE1 protein and associated heme. As determined from monophasic exponential decay curves, IIE1 protein and heme half-lives (26–28 h and 17 h, respectively) did not differ between the treatment groups. However, IIE1 synthesis rates tended to be higher in ethanol-treated rats than in controls, suggesting that enzyme stabilization is not involved.

In conclusion, our results indicate that IIE1 protein induction by ethanol involves increased enzyme synthesis in both hamsters and rats. Enhanced IIE1 synthesis in hamsters is most likely due to induction by ethanol of IIE1 mRNA while in rats, ethanol may increase IIE1 mRNA translational efficiency.

Cardiology

Normalization of Left Ventricular Mass and Associated Changes in Neurohormones and Atrial Natriuretic Peptide after One Year of Sustained Nifedipine Therapy for Severe Hypertension. Robert A Phillips, Maria Ardeljan, Seiichi Shimabukuro, Martin E Goldman, David L Garbowit, Howard B Eison, Lawrence R Krakoff, Divisions of Hypertension and Cardiology, Mount Sinai Medical Center, Box 1085.

Sixteen patients with severe hypertension were treated for one year with extended release nifedipine during which serial changes in left ventricular mass index (LVMI) and associated alterations in LV systolic function, LV filling, plasma renin activity (PRA), atrial natriuretic peptide (ANP) and catecholamines were evaluated. Blood pressure (BP) was significantly reduced from 200 ± 8/122 ± 3 mm Hg (mean ± SE) to 144 ± 6/87 ± 1 ($p < 0.0001$) at one year. After six months LVMI was significantly reduced by 19% from 121 ± 8 to 96 ± 7 gm/m^2 and this reduction was sustained at one year. Septal and posterior wall thickness were reduced from 12.8 ± 0.1 to 10.0 ± 0.03 mm and from 13.4 ± 0.1 to 11.2 ± 0.04 mm ($p < 0.001$), respectively. At entry 63% of subjects had LV hypertrophy (LVH), whereas at one year only 25% had LVH. LV fractional shortening (FS) increased from 34% to 42% ($p < 0.05$) and the relationship between FS and end-systolic stress did not change. Over the year of sustained BP reduction the peak velocity of early filling increased from 58 to 63 cm/sec ($p = 0.07$), peak velocity of late filling did not change, and the A/E ratio significantly decreased ($p < 0.05$). Plasma ANP, markedly elevated at entry, decreased from 70 ± 15 to 41 ± 8 pg/ml at one year ($p < 0.05$). PRA and catecholamines were not altered.

Conclusion: Treatment of severe hypertension for one year with sustained-release nifedipine is accompanied by LV mass regression, maintenance of LV systolic function, reduction of atrial natriuretic peptide and no detectable activation of either the sympathetic or renin systems.

Natural History of Aortic Regurgitation Studied with Serial Radionuclide Angiography. Josef Machac, Deborah Matza, Dimitrios Alexopoulos, Raymond Gibbons, Martin E Goldman, Steven F Horowitz, Division of Cardiology, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029, and The Mayo Clinic, Rochester, MN.

To better understand the progression of disease in well patients (Pts) with aortic regurgitation (AR), we followed 32 Pts with pure AR using rest (Rest) and exercise (Ex) gated blood pool imaging at baseline (T0), one year (T1), and in a smaller subgroup (N = 20), at two years (T2). Pts were evaluated for changes in LVEF and RVEF (in %), workload in watts (Work) and NYHA class.

At T1, there was no significant change in Rest LVEF, Ex LVEF, Rest RVEF, Ex RVEF, Work or NYHA. Two Year Follow-Up:

Natural History of Aortic Regurgitation Studied with Serial Radionuclide Angiography (*continued*)

	T0	T1	T2	p
Rest LVEF	59 ± 9	59 ± 7	55 ± 8	0.02
Ex LVEF	59 ± 13	59 ± 13	55 ± 13	0.02
Rest RVEF	44 ± 14	42 ± 11	40 ± 9	NS
Ex RVEF	54 ± 14	53 ± 13	48 ± 13	0.01
Work	131 ± 36	134 ± 48	135 ± 50	NS
NYHA	1.6	1.4	1.2	NS

In 2 years Rest and Ex LVEF and Ex RVEF declined despite absence of clinical or workload changes. This suggests that in these Pts with a mean flat response to exercise, there is a gradual but mild decrease in measured function.

Clinical Immunology

Interleukin 6 Transcription by Human Airway Epithelial Cells. TH Kalb, EJ Siden, ZM Marom, L Mayer, Divisions of Pulmonary and Critical Care Medicine, and Clinical Immunology, Box 1232, Mount Sinai School of Medicine, New York, NY.

Human airway epithelial cells (AEC) have been shown to stimulate allogeneic T lymphocytes in mixed lymphocyte responses (MLR). Since the proliferation of T cells in such cultures is dependent on the presence of cytokines including IL-1 and possibly IL-6, we examined human airway specimens for the transcription of IL-1-beta and IL-6 by in situ hybridization.

RNA probes were prepared from cDNA clones [IL-1-beta ATCC p067024/IL-6 Cetus 3ZIL62] in Gemini vectors. ^{35}S labeled sense and anti-sense RNA transcripts were generated with SP6 and T7 polymerase following linearization. Frozen section of bronchial segments, and dissociated cell cytospin preparations were obtained from thorocotomy specimens. LPS [500 ng/ml] stimulated peripheral blood monocytes served as controls. No message for IL-1-beta in the epithelium was detected. However, AEC-specific IL-6 transcripts were detected by autoradiography in three of seven frozen section specimens, as well as ¾ cytospin preparations, suggesting that this cytokine may provide proliferative stimulus in AEC driven MLR.

Since IL-6 has multiple actions which include generation of the acute phase response, the regulation of IL-6 transcription in AEC may be relevant to the expression of inflammation in the lung.

Effects of In Vitro PEG-IL-2 Treatment in CVI. C Cunningham-Rundles, L Mayer, Lois Tuerk-Mendelson, Clinical Immunol/Med, Mount Sinai Medical Center, One Gustave Levy Place, NY, NY, 10029.

Patients with common variable immunodeficiency (CVI) often have substantial T cell defects, accompanied by reduced IL-2 production. The in vitro T cell defects can be corrected by the addition of IL-2 to cell cultures; in these studies increased immunoglobulin secretion has been detected. We have previously shown that stimulation of CVI T cells with anti CD3 monoclonal antibodies, or the addition of T cell supernatants containing B cell differentiation factors can also enhance antibody production in vitro in CVI. Thus the concept of an irrevocable intrinsic B cell defect, to explain the hypogammaglobulinemia in all patients with CVI, is probably not valid. Ig deficiency could result from improper communication between CVI T cells and autologous B cells.

Because of these findings, we started a clinical trial in CVI using a new biologic, human recombinant IL-2 conjugated to polyethylene glycol, obtained from Cetus Corporation. This coupling procedure results in an IL-2 with a greatly increased half-life, with little loss of biologic activity. Six adult patients tested in vitro had a strong proliferative response to PEG-IL2 (1, 10, 100 and 1000 IU/ml) used alone or in combination with PHA and are thus candidates for in vivo treatment. Four patients have been enrolled in a twelve week dosage escalation protocol in which 250,000 to 10^6 IU/m^2 is given IV weekly. During treatment enhanced lymphocyte proliferative responses to mitogens or antigens, and increased levels of soluble IL-2 receptor have been demonstrated for two patients. The B cells of one patient who had repeated displayed lack of immunoglobulin secretion in vitro produced normal levels of immunoglobulin in vitro after 4 weeks of treatment evaluating T lymphocyte functions, soluble IL-2 receptors, and in vitro Ig production in response to SAC/IL-2, EBV, IL-6, and BCDF.

Our hypothesis is that T cell stimulation in vivo may improve T cell functions in CVI (as has been previously shown in 5/6 patients with other severe T cell defects) and that B cell differentiation may be enhanced.

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Endocrinology

Effect of Sex Steroids and Their Antagonists on the Growth and Cell Cycle Kinetics of LNCaP Human Prostate Cencer Cells. AC Levine, D Drafta, A Maran, C Chang† and A Kirschenbaum, Mount Sinai School of Medicine, CUNY, New York, NY 10029 and †University of Chicago School of Medicine, Chicago, IL 60637.

The human prostate cancer cell line LNCaP was originally isolated from the lymph node of a man with metastatic prostate cancer that was unresponsive to hormonal treatment. In vitro, however, the cells have been shown to be sensitive to androgens and estrogens.

LNCaP cells were grown in RPMI media with 5% charcoal-treated fetal bovine serum at a concentration on 4×10^4 cells/well in 24 well plates. The effects of dihydrotestosterone (DHT), estradiol (E_2), the anti-estrogen hydroxytamoxifen (TAM) and the anti-androgen hydroxyflutamide (FLU) on cell proliferation were measured via cell counts (hemocytometer), DNA content and ^{3}H-thymidine uptake. DHT, E_2 and FLU, given separately, stimulated cell growth significantly ($2-3\times$) over control while TAM had no effect. Maximal growth stimulation was seen with DHT 1 nM, E_2 100 nM and FLU 1 microM. The combination of DHT and FLU resulted in the same growth stimulation as FLU alone. The addition of TAM to E_2 did not inhibit the proliferative effects of E_2 alone. Flow cytometric analysis revealed that DHT, E_2 and FLU increased the percentage of cells in S phase whereas TAM had no effect. There were no estrogen receptors detectable by immunohistochemistry (ERICA kit, Abbott Labs). Androgen receptors were demonstrable (monoclonal antibody, C. Chang). Binding studies using the synthetic androgen methyltrienolone (R1881) revealed that dihydrotestosterone, flutamide and estradiol bound significantly to the androgen receptor. Tamoxifen did not exhibit specific androgen receptor binding.

We conclude that LNCaP cells proliferate in response to dihydrotestosterone, estradiol and hydroxyflutamide. As these cells contain nuclear androgen receptors, but no demonstrable nuclear estrogen receptors, it is probable that the proliferative effects of these 3 compounds are mediated via the androgen receptor. In addition, the observation that hydroxytamoxifen neither inhibits nor enhances the proliferative effects seen with E_2 is further evidence that the E_2 effects are not mediated via the E_2 receptor. The androgen receptor in this cell line, and possibly in other prostate cancers which have become hormone resistant, may be altered and responsive to many sex steroids and their antagonists.

Effect of the Addition of Tamoxifen to Leuprolide Therapy on Prostate Size and Serum PSA Levels in 3 Men with Benign Prostatic Hypertrophy. Alice C Levine, Alexander Kirschenbaum, and J Lester Gabrilove, Mount Sinai Medical Center, New York, NY.

We have previously reported that treatment with a long-acting GnRH analogue (leuprolide) reduced prostate size and symptoms of prostatism in 15 men with benign prostatic hypertrophy (BPH). In addition, serum prostate specific antigen (PSA) levels fell dramatically in 12 men tested during leuprolide treatment.

In 3 men with BPH on leuprolide therapy for >1 year we added an anti-estrogen, tamoxifen 10 mg p.o. b.i.d. to their regimen. All 3 men reported worsening of hot flushes but no change in the symptoms of prostatism with tamoxifen. However, in all 3 men prostate size measured by transrectal ultrasound increased during tamoxifen treatment (average increase 15% after 2–3 months addition of tamoxifen). Serum PSA levels in the 2 men who all ready had low levels (<0.5 ng/ml) on leuprolide treatment, did not rise with the addition of tamoxifen. The 3rd man, however, had a decrease in his serum PSA levels with the addition of tamoxifen (from 5.6 ng/ml on leuprolide alone to 2.1 ng/ml with leuprolide plus tamoxifen).

We conclude that the addition of tamoxifen to leuprolide therapy in 3 men with BPH resulted in an increase in prostate size. Serum PSA levels either remained low or fell with the addition of tamoxifen in spite of the increase in prostate size. We postulate that tamoxifen increases stromal volume and decreases epithelial cell secretory function in men with BPH. It is as yet unknown whether this is an anti-estrogenic or pro-estrogenic effect of tamoxifen.

Induction of Human Thyroid Cell ICAM-1 (CD54) Antigen Expression and ICAM-1 Mediated Lymphocyte Binding. A Martin, GK Huber, and TF Davies, Department of Medicine, Mount Sinai School of Medicine, New York, NY 10029.

To further understand the mechanism of lymphocyte accumulation within the thyroid gland in autoimmune thyroid disease we have examined the expression, regulation and functional significance of the intercellular adhesion molecule-1 (ICAM-1, CD54) in human thyroid monolayer cells and immortalized thyroid cell clones.

Human thyroid monolayer cells derived from both normal and abnormal human thyroid tissue showed low basal expression of the ICAM-1 antigen flow cytometric assessment (mean % ± SD positive cells = 13.7 ± 6.1) compatible with the presence of ICAM-1 positive non-thyroid cells within the monolayer cultures. However, thyroid cell ICAM-1 antigen expression was further induced by exposure to recombinant human gamma interferon (IF). 100 U/ml of gamma IF induced ICAM-1 expression in 56.0 ± 19.0% of thyroid monolayer cells. Even greater expression of ICAM-1 antigen was induced by gamma IF in human fetal thyroid cell monolayers of high purity (up to 80% of ICAM-1 positivity), Graves' thyroid monolayers (up to 84%), and in two immortalized human thyroid cell clones, 12S and TAD-2 (up to 61%). Furthermore, dose-response curves for ICAM-1 and HLA-DR antigen induction by increasing concentrations of gamma IF showed that ICAM-1 antigen gene induction was 10-fold more responsive to gamma IF than the HLA-DR antigen gene.

In order to explore the functional consequence of ICAM-1 antigen expression by thyroid epithelial cells we examined the binding of peripheral blood mononuclear cells (PBMC) to autologous thyroid monolayer cells and immortalized thyroid cells. These studies revealed a preferential adhesion of human PBMC to gamma-IF treated thyroid monolayers compared to untreated control monolayer cells. Furthermore, this gamma IF induced cell adhesion was specifically inhibited by monoclonal anti-ICAM-1.

These experiments demonstrate not only the capacity of human thyroid epithelial cells to express ICAM-1 antigen in the presence of a cytokine but, in addition, identify ICAM-1 antigen as responsible for enhanced T cell binding to thyroid epithelial cells. ICAM-1 antigen may, therefore, play an important role in T cell targeting and accumulation within the thyroid gland in autoimmune thyroid disease.

Absence of LH Receptor in the Rat Thyroid: Evidence for Specificity Crossover at the TSH Receptor Level. PN Graves and TF Davies, Department of Medicine, Mount Sinai School of Medicine, New York, NY 10029.

Human chorionic gonadotropin (hCG) and purified LH interact with intact thyroid tissue and isolated thyroid cells to induce secretion of cyclic AMP, thyroid cell growth, and release of thyroid hormones. Similarly, patients with high serum hCG levels secondary to choriocarcinoma may be thyrotoxic.

We have attempted to explain this phenomenon by the presence of aberrant LH receptors within the thyroid interacting with gonadotropin. Thyroid tissue is known to contain several members of the G protein-coupled receptor subfamily and the LH receptor (LH-R) may be amongst them. Sequences encoding the transmembrane domains of this subfamily are highly conserved. Domains #3 and #6 of the rat LH-R were targeted for PCR amplification using cDNA from our TSH and hCG-responsive 1B-6 subclone of Fisher rat thyroid cells (FRTL-5) as template and oligonucleotides based on published rat LH-R sequences within these domains. cDNA from an LH-R positive control tissue (testis) was efficiently amplified under stringent annealing conditions giving a 464 bp product as predicted. However, using thyroidal cDNA no amplification occurred under such stringent conditions indicating the absence of LH receptor mRNA in these cells. By contrast, under non-stringent conditions, a product appeared whose sequence differed from the rat LH receptor and is likely to represent the rat TSH receptor.

These data indicate that specificity crossover between LH/hCG and TSH occurs at the TSH receptor.

A Second Thyroglobulin mRNA (hTg-2) Exists in Human Thyroid. PN Graves and TF Davies, Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

Thyroglobulin (Tg) is the major polypeptide produced by the thyroid gland and is the ubiquitous source of thyroid hormones in vertebrates. The 330kd Tg monomer is encoded by a 9kb Tg mRNA, sequenced in several mammalian species. We recently reported the presence of a truncated 1kb Tg mRNA in the rat (rTg-2 mRNA) which contained only the 5′ end of 9kb Tg mRNA followed by additional coding and noncoding sequences not found in 9kb Tg mRNA (Mol. Endocrinol. 1990, 4:155). rTg-2 mRNA was thyroid-specific, polyadenylated, cytoplasmic, and regulated by TSH.

We now report the presence of a second Tg transcript (hTg-2 mRNA) in human thyroid tissue. As in the rat, the 1kb hTg-2 mRNA was similar to 9kb Tg mRNA at its 5′ end but dissimilar at the 3′ end. The 3′ ends of both species showed 98% nucleotide homology and encoded identical 29 amino acid sequences. The 5′ end of hTg-2 mRNA was colinear to exons 1–5 of 9kb Tg mRNA but contained many base substitutions. Hence, 9kb Tg mRNA and hTg-2 mRNAs may be products of two different genes rather than the result of alternative splicing. Further, since the hTg-2 gene encodes two of ten tandem repeat units comprising the N-terminal half of 330kd Tg, as well as tyrosines known to be hormonogenic in 330kd Tg, it may represent the evolutionary progenitor of the gene encoding 330kd Tg.

Since the hTPO and hTSH receptor genes have previously been demonstrated to exhibit more than one mRNA, our data reveals a general rule that each of the thyroid specific antigens known to be involved in thyroid autoimmune responses is potentially heterogeneous. Such diversity may influence the propensity for immune challenge and thyroid autoimmune disease. The strict conservation of TSH regulated hTg-2 and rTg-2 mRNAs, which include hormonogenic tyrosine loci, is likely to be indicative of an important role for the putative polypeptide products in normal thyroid physiology.

Evidence for T Cell Mediated Postpartum Thyroid Dysfunction: Results from a Prospective Study in New York City. A Stagnaro-Green, SH Roman, R Cobin, TF Davies, Division of Endocrinology, Box 1055 Mount Sinai School of Medicine, New York, NY 10029.

Thyroiditis is a T cell mediated disease yet little is known about T cell subset changes in relation to the onset of post-partum thyroid disease

Evidence for T Cell Mediated Postpartum Thyroid Dysfunction: Results from a Prospective Study in New York City (*continued*)

(PPTD). As part of a prospective study of PPTD we screened 552 women in the first trimester of pregnancy for thyroid autoantibodies (anti-TPO & anti-hTg) by highly sensitive ELISAs and found 19.6% of women to be thyroid autoantibody positive (Ab+). Thirty-nine Ab+ and 20 antibody (Ab)− women were studied prospectively until six months PP by monitoring their thyroid function, autoantibody levels and T cell subset changes. During pregnancy, in these 68 women, there were no significant alterations in CD4+ (helper), CD8+ (suppressor-cytotoxic), CD4+2H4+ (suppressor-inducer) or T cells expressing MHC class II antigens as a marker for T cell activation (CD4+DR+ & CD8+DR+) in comparison to normal age matched non-pregnant controls ($n = 33$). In the PP period, compared to the third trimester, both Ab+ and Ab− groups of women demonstrated a marked increase in CD4+2H4+ T cells (from 11.2 ± 0.95% to 18.0 ± 0.01%, $p = 0.0001$). In addition, the % CD8+ T cells demonstrated a similar marked increase (from 26.4 ± 0.88% to 30.5 ± 0.48%, $p = 0.0001$) when compared to the third trimester data. However, only the Ab+ group of women demonstrated evidence of increased T cell activation in the PP period (as revealed by an increase in HLA-DR+ T cells compared to third trimester levels for both CD4+DR+, 1.50 ± 0.16% vs. 2.74 ± 0.38%, $p < .01$, and CD8+DR+ cells 1.11 ± 0.18% vs 2.34 ± 0.39%, $p < .01$). This occurred at the time when T cell subsets were changing and thyroid autoantibody levels were at a peak. Eleven women developed PPTD, of whom 10 had thyroid autoantibodies at initial screening (26% of Ab+ group), and all exhibited similar T cell changes.

In conclusion, these prospective data show marked enhancement of suppressor-cytotoxic (CD8+) T cells in the PP period of normal pregnancies which appeared to be mediated by enhanced suppressor-inducer (CD4+2H4+) T cells. The subsequent development of thyroiditis in the PP period, a time of enhanced immune activity, is primarily dependent upon the antigen-specific T cell repertoire.

N-Methyl-D,L-Aspartic Acid (NMDA)-Induced LH Release in Hypogonadal Female Mice with Fetal Preoptic Area Grafts (HPG/POA).

Youichi Saitoh, Ann-Judith Silverman, and Marie J Gibson, Division of Endocrinology, Mount Sinai School of Medicine, New York, NY, 10029.

To clarify the mechanism of NMDA-induced LH release, normal and HPG/POA female mice were challenged by venous injection of the excitatory amino acid. Most HPG/POA mice entered persistent estrus and had ovarian and uterine development by 60 days after graft surgery; a few showed ovarian cyclicity after pregnancies induced by reflex ovulation. One group of normal and HPG/POA female mice were ovariectomised (OVEX); a second group were OVEX and estrogen primed (OVEX/E2), and a third group included intact cycling normal and cycling HPG/POA that were tested in the estrous state. After blood sampling via intrajugular catheters, HPG/POA were perfused for light and/or electron microscopic immunohistochemical studies.

There were significant increases in plasma LH 10 min after NMDA challenge in normal OVEX (baseline: 0.58 ± 0.20; +10 min: 1.85 ± 0.41 ng/ml) and OVEX/E2 (baseline: 0.33 ± 0.02; +10 min: 0.80 ± 0.21 ng/ml). HPG/POA OVEX/E2 mice ($n = 7$), which had 4–12 GnRH cells and GnRH axonal outgrowth, responded to NMDA with increased LH (baseline: 0.36 ± 0.03; +10 min: 1.03 ± 0.24 ng/ml). HPG/POA OVEX/E2 mice ($n = 5$) with sparse GnRH fiber outgrowth did not respond to NMDA. Neither normal estrous or cycling HPG/POA estrous mice responded to NMDA.

These results suggest that NMDA stimulation of GnRH cells is estrogen-sensitive and may be mediated by interneurons.

Supported by NIH grants NS20335 and HD19077.

Molecular Mechanisms of T Cell Activation: Dissociation between Class II, Tac, and Proliferation.

Silvia Salvadori and Karen S Zier, Division of Endocrinology, Mount Sinai School of Medicine, Box 1055.

T cell activation involves a complex series of events, which can be defined in many different ways. Among the most common changes from the resting to the activated state are increased steady state levels of mRNA for a variety of cell surface determinants, including MHC class II antigens (DR, DP, and DQ), the p55 IL-2 receptor, Tac, and the induction of proliferation. Our laboratory is interested in the regulation and functional role of MHC class II determinants on activated human T cells. In order to define the pathways operative during T cell activation, we tested the ability of various modes of stimulation to induce the expression of class II, Tac, and to stimulate proliferation.

Stimulation of purified T cells for 3 days with the phorbol ester, PdB, and the calcium ionophore, ionomycin, with or without the presence of accessory cells (AC), induced strong proliferation and Tac expression, but only low levels of DR as determined by flow cytometry. In contrast, stimulation of purified T cells with PHA stimulated weak proliferation, strong Tac expression, but generally higher class II levels. When T cells with AC were stimulated with PHA, class II, Tac, and proliferation all were strongly induced. Further culture in conditioned medium of day 3 T cells previously activated with either PdB and ionomycin or with PHA resulted in increased class II levels. Additional experiments suggested that neither IL-2, nor gamma-interferon was responsible.

These results demonstrate that in purified T cells stimulated with PdB and ionomycin, expression of class II is separable from the induction of proliferation and the upregulation of Tac. They are consistent with the hypothesis that an increase in calcium levels and the activation of PKC are not sufficient to induce class II. Moreover, they suggest the binding of ligand to a surface receptor or secretion of a co-stimulatory factor, perhaps by AC, may be necessary.

Molecular Basis for Class II Expression in Activated T Cells.

Howard S Caplen and Karen S Zier, Mount Sinai School of Medicine, Division of Endocrinology, Box 1055.

The activation of normal T cells involves a series of events resulting in the acquisition of a number of functional properties not associated with resting T cells. During this process T cells express a number of activation antigens, among them Tac, and HLA-class II DR, DP, and DQ. Although class II molecules play a pivotal role in regulating the immune response, their role in T cell function is unknown. We previously reported that class II surface levels were first detected on purified T cells as early as 30 minutes following stimulation with PHA and PMA, well before the initiation of DNA synthesis, and that levels increased with time. Using Northern or dot blots class II mRNA accumulation was detected weakly 15 minutes after stimulation and strongly by 24 hours. Immunoblot analysis of lysates from resting T cells using an anti-DR monoclonal antibody detected a polypeptide of ~28 kDa and a similar band of greater intensity in activated cells. One hypothesis to explain these results was that there were two levels of class II regulation in T cells.

To test this, we used Northern blot analysis to measure DR mRNA steady state levels in resting T cells. We observed that low levels of mRNA for DR were detectable which increased in intensity after activation. Next, we looked at transcription of class II in resting cells using nuclear run-on assays. Transcripts for DR, DP, DQ, and DZ were detected in cells which were neither dividing nor transcribing IL-2 or Tac. Transcripts for DO were not detected.

These results suggest that resting T cells may synthesize low levels of class II antigens, but either retain them in cytoplasm or do not orient them in the membrane in a detectable way until following activation. After activation, gene expression increases, resulting in upregulation of both class II mRNA and surface antigens. The finding of class II transcription in resting cells suggests that increases in class II levels after activation involve post-transcriptional regulation, at least in part. Finally, the absence of DO demonstrates that class II products are not coordinately expressed in T cells.

Negative Signal Transmission through Class II Molecules on Activated T Cells.

Nancy D Urban and Karen S Zier, Division of Endocrinology, Mount Sinai School of Medicine, Box 1055.

The MHC class II antigens, DR, DQ, and DP in man, are cell surface heterodimers consisting of a 30–34 kD α, or heavy chain, and a 26–28

Negative Signal Transmission through Class II Molecules on Activated T Cells *(continued)*

kD β, or light chain. They are expressed on human T cells following activation, but their functional role remains obscure. The importance of MHC class II antigens in regulating immune responses has been appreciated for many years. It is generally believed that they help to determine whether an animal is able to respond to a particular antigen by influencing cooperation between antigen presenting cells and helper T cells. More recently evidence has accumulated that they also may serve a functional role on B lymphocytes by transducing signals. In addition it has been reported that monoclonal antibodies directed against DR antigens on T cells were able to inhibit proliferation, suggesting that they might be involved in signal transduction in T cells as well.

The present study was undertaken in order to investigate the basis for the inhibition of T cell proliferation by anti-class II antibodies reacting solely with responder T cells and not at the level of the stimulator. We have investigated the effect of anti-class II monoclonal antibodies on T cell proliferation. We report that monoclonal antibodies directed against all three class II products, DR, DQ, and DP, can inhibit T cell proliferation. In addition, while inhibition of proliferation triggered with rIL-2 was dramatic, only very modest inhibition by anti-class II monoclonals was seen when cells were activated by using PdB and ionomycin. Anti-class I monoclonals, on the other hand, inhibited both interactions equally well, attesting to the specificity of these results.

Studies of the underlying mechanism indicated that inhibition could not be ascribed to the downregulation of the p55 IL-2 receptor, Tac, or to an inadequate supply of IL-2. Furthermore, proliferation could be interrupted even when anti-class II antibodies were added to cycling cells, suggesting that early events were not specifically targeted. Our findings are consistent with the hypothesis that class II determinants on T cells may be among the cell surface determinants involved in the transduction of signals which influence proliferation.

Ontogeny, Mechanisms, and Heterogeneity of Androgen Action on the Hypothalamic-Pituitary Axis of Women. D Shelley, A Dobrjansky, W Futterweit, A Dunaif, Mount Sinai School of Medicine, New York, NY 10029.

The effects of androgens on the female gonadal axis remain unclear but are of considerable interest because of the gonadotropin secretory disturbances that occur in hyperandrogenic conditions such as the polycystic ovary syndrome (PCO).

We examined LH/FSH release in 5 female-to-male transsexuals (TS1-TS5) ages 18–45 during gender reversal with testosterone (T) enanthate, 400 mg im q 3 wks. Blood samples for LH/FSH were obtained q 10 min for 8 h and 2 h after GnRH, 10 ug IV, in the follicular phase (fp) basally, at 3–18 mons (Rx$_1$), and at 9–15 mons (Rx$_2$). Each TS served as her own control; results were also compared to 5 normal ovulatory women (NLs) in the fp. The effect of a non-aromatizable androgen were determined by oral administration of fluoxymesterone 10 mg/d for 20–30 days in TS3 and TS4. Basal LH/FSH release and sex hormone levels in the TSs were similar to NLs. During therapy, T levels were in the normal male range, and estradiol (E$_2$) levels were in the early fp range. The initial action of T was a significant increase in GnRH sensitivity (mean ± SEM, LH basal 272 ± 93 vs Rx$_1$ 502 ± 110 ug/L LER 907, $p < 0.05$). Chronic T therapy (10–18 mons) markedly increased mean LH levels (basal 47, 61 vs Rx$_2$ 100, 130 ug/L) and LH pulse amplitude (basal 18, 39 vs Rx$_2$ 89, 64 ug/L) in TS2 and TS5, respectively. Conversely, by Rx$_2$, TS1 and TS3 showed suppression of LH release. LH pulse frequency slowed by Rx$_2$ in all subjects except TS5. Chronic fluoxymesterone therapy further suppressed all parameters of LH/FSH release without changing responses to GnRH.

Conclusions: 1) T can alter LH/FSH release producing changes similar to PCO, but this requires months of exposure and considerably higher androgen levels than those observed in PCO. 2) The initial effect of chronic T exposure is to increase gonadotropin sensitivity to GnRH; this occurs before changes in pulsatile release and appears to be secondary to aromatization to E$_2$ rather than a direct T effect. 3) Angrogens can also directly inhibit LH/FSH release. 4) Despite similar serum T levels, responses to chronic T therapy are heterogeneous.

Thyroid Hormone Increases "Insulin-Regulatable" Glucose Transporter Gene Expression in Rat Skeletal Muscle. Steven P Weinstein, Julie Watts, and Richard S Haber, Division of Endocrinology, Box 1055, Mount Sinai School of Medicine.

The facilitated diffusion of glucose into cells is mediated by a family of related glucose transport proteins, which differ in their tissue distribution. These include the ubiquitous erythroid glucose transporter, the liver glucose transporter, and the muscle/fat ("insulin-regulatable") glucose transporter, which mediates insulin-stimulated glucose uptake. Although the regulation of glucose transporter genes is of importance with respect to both normal physiology as well as pathophysiological states such as diabetes mellitus, the factors influencing the expression of these recently described tissue-specific forms of the glucose transport protein are not well understood.

The enhancement of metabolic rate by thyroid hormone in target tissues is accompanied by an increase in glucose utilization. In many tissues, including skeletal muscle, membrane transport is rate-limiting for glucose uptake, and increased glucose utilization requires an enhancement of glucose transport across the plasma membrane. To determine the effects of thyroid hormone on glucose transporter gene expression, we have studied the regulation of glucose transporter isotypes in rat skeletal muscle, a tissue in which thyroid hormone enhances metabolic rate, and in brain, in which metabolic rate is not affected.

Treatment of hypothyroid rats with T$_3$, 100 ug/100 g BW/day for 6 days, increased the abundance of the muscle/fat glucose transporter protein in crude membranes from hindlimb muscle, assessed by immunoblotting, to 145 ± 8% of control in animals fasted for 17–20 hours prior to sacrifice, and to 159 ± 16% of control in animals fed *ad libitum* (means ± SE). In purified plasma membranes, this effect of thyroid hormone was greater (208 ± 23% and 219 ± 13% of control in fasted and fed animals, respectively). Levels of muscle/fat glucose transporter mRNA were also increased in hindlimb muscle from the T$_3$-treated rats to 261 ± 17% and 316 ± 23% of control in fasted and fed animals, respectively. In contrast, the erythroid glucose transporter protein and its mRNA, which are only weakly expressed in skeletal muscle but strongly expressed in brain, were not substantially increased by T$_3$ treatment in either tissue. Thyroid hormone may thus be an important regulator of the muscle/fat glucose transporter in skeletal muscle.

Absence of Effect of Mild and Severe Hyperandrogenemia on Detection of Thyroid Autoantibodies in Reproductive Age Women. Sheila H Roman, Essam El-Harazy, and Walter Futterweit, Division of Endocrinology, Box 1055 Mount Sinai School of Medicine, NY, NY 10029.

Both autoimmune thyroid disease and the propensity for thyroid autoantibody (T-Ab) production have a distinct female preponderance. In order to examine the potential effect of acute and chronic hyperandrogenemia on T-Ab production, we have measured thyroglobulin and thyroid microsomal autoantibodies by sensitive ELISA techniques in the following groups of reproductive age women: 1) euthyroid ovulatory women (n = 36) without clinical evidence of thyroid disease, 2) women (n = 77) with polycystic ovary syndrome (PCO), and 3) female to male (f-m) transsexuals (n = 15) prior to (pre) and during (post) testosterone enanthate (TE) therapy. There were no significant differences in the frequencies of detectable T-Ab between the control women and women with PCO despite significant differences in serum testosterone (T):

	Age (yrs)	T (ng/dL)	p	T-Ab positive	p
Controls	28 ± 1.0*	39 ± 3.2	0.01	6/36 (16.7%)	NS
PCO	27 ± 0.5	72 ± 3.9		13/77 (16.8%)	

* Mean + SEM

Of the 15 f-m patients, 4/15 (26.7%) had detectable thyroid autoantibodies prior to exogenous administration of 400 mg TE I.M. every 3 weeks. The mean duration of TE therapy was 18 ± 3.4 months (range 3–46). There were no significant changes in the titers of T-Ab during treatment with TE despite a mean serum T level >1000 ng/dL.

Absence of Effect of Mild and Severe Hyperandrogenemia on Detection of Thyroid Autoantibodies in Reproductive Age Women *(continued)*

	Age (yrs)	T (ng/dL)	p	T-Ab titers	p
f-m (pre)	27 ± 0.3*	54 ± 5.1	0.0002	0.19 ± 0.1	NS
f-m (post)		1018 ± 189.4		0.20 ± 0.01	

* Mean + SEM

We conclude: 1) Mild chronic hyperandrogenemia does not alter the frequency of thyroid autoantibody detectability in reproductive age women. 2) Administration of male serum levels of TE to reproductive age women does not affect thyroid autoantibody titers. 3) Hyperandrogenemia in women does not appear to alter the immunopathogenesis of thyroid autoantibody production.

Gastroenterology

How the Parietal Secretion Crosses the Gastric Mucus without Being Neutralized. TL Fabry, Division of Gastroenterology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

The gastric epithelium is covered with a highly viscous, polysaccharide containing mucus, which is possibly part of the protective mechanism against acid damage. Ions and water can freely diffuse through this layer, but acid would be neutralized during its diffusion through the mucus. Therefore parietal secretion reaches the luminal surface of the stomach by a mechanism other than diffusion through the mucus layer. Viscous fingering instability is a hydrodynamic phenomenon, where a low viscosity fluid (water) passes through a high viscosity layer without mixing.

It is proposed that parietal secretion forms viscous fingers through the mucus layer to enter the gastric lumen. Model: The gastric mucus is a high viscosity non-newtonian fluid. The parietal secretion forms a spherical droplet under this layer in the opening of the gastric pit. Because of the spherical interface, the interfacial tension is low: this results in a fractal growth phenomenon (Nittman et al, Nature 314, 141–144, 1985) of aqueous fingers through the mucus. On the lumen side of the mucus the acid layer is planar: i.e., the interfacial tension is high and no fingers will form. The requirements for this model are: 1. the viscous layer is a non-newtonian fluid (passage through a hydrophobic layer of newtonian fluid would be a non-fractal, energy requiring process) 2. the interfacial tension is different on both sides of the mucus layer. Experimental: In the model system we placed a drop of pH 1, HCl colored with phenol red under a layer of 50% Stractan (a viscous, non-newtonian polysaccharide solution). The system was photographed laterally. At random intervals, the drops formed a viscous finger to pass the mucus layer.

Conclusion: Parietal secretion crosses the gastric mucus in bulk, rather than by diffusing through it.

General Medicine

Depressor Responses to the Visit Identify Essential Hypertensives with Greater Target Organ Damage. Cheryl L Laffer and Fernando Elijovich, Division of General Internal Medicine, Mount Sinai School of Medicine, 1200 Fifth Avenue, New York, NY 10029.

The pressor or depressor responses to the medical visit observed in hypertensive patients lead to over or underestimation of their "true" (integrated over time) blood pressure (BP). To assess whether this determines different degrees of target organ damage, we studied 7 patients with depressor responses (D) and 7 with pressor responses (P) matched for: office BP (173 ± 12/106 ± 1 vs 171 ± 8/103 ± 2 mmHg), duration of hypertension (14 ± 2 vs 15 ± 3 years), age (50 ± 4 vs 52 ± 3 years) and sex. BP responses (D = −7 ± 2/−2 ± 2, P = 21 ± 5/9 ± 1, $p < 0.001$) were calculated as clinic-related minus clinic-unrelated (daytime) readings of 24 hr ambulatory monitors, after 3 weeks on placebo. Daytime average BP was higher in D (173 ± 9/107 ± 6) than in P (154 ± 5/99 ± 3), but not significantly. EKG score for LVH by Estes' criteria was higher in D (2.7 ± 0.8 vs 0.3 ± 0.2, $p < 0.03$). Retinopathy grade II was present in 4/7 D and 0/7 P ($p < 0.04$, Fisher's exact test). Serum creatinine and creatinine clearance did not differ between D and P. D had higher weight (196 ± 10 vs 161 ± 9 lb, $p < 0.02$), BMI (36 ±1 vs 30 ±1 kg/m^2, $p < 0.01$) and blood glucose (184 ± 35 vs 103 ± 10 mg%, $p = 0.06$). In conclusion: our patients with D had more cardiovascular but not renal target organ damage. This may be due to: 1) underestimation of their "true" BP by office BP or 2) associated obesity/diabetes determining both target organ damage and a depressor response to the visit.

Hematology

Erythropoiesis in Hemoglobinopathies. Rona S Weinberg, Patricia Giardina, and Blanche P Alter, Mount Sinai School of Medicine, One Gustave L. Levy Place, Polly Annenberg Levee Division of Hematology, Box 1079 NY, NY and New York Hospital-Cornell Medical Center, NY, NY.

The purpose was to characterize β-thalassemia major (TM) and β-thalassemia intermedia (TI), and sickle cell (SS) erythroid progenitor cells (BFU-E), and to compare them with fetal (FB), newborn (NB), and normal adult (AA).

Peripheral blood mononuclear cells (MNC), were cultured in methyl cellulose with erythropoietin (Ep) for 21 days. No colonies were observed without the addition of Ep. TM, TI, and AA bursts required similar doses of Ep to achieve ½ maximal growth (0.62, 0.46, and 0.74 units Ep/ml, respectively). FB, NB, and SS bursts tended to be more sensitive to Ep, requiring lower doses of Ep to achieve ½ maximal growth (0.33, 0.33, and 0.31, respectively). In all TI (6/6), and most TM (9/10), NB (7/9), and AA (30/34) cultures, maximal growth occurred by day 16. In contrast, maximal growth was earlier in FB cultures (6/10 by day 13) and later in SS cultures (8/22 required 20 days). The mean day of maximal colony growth was 13.8 in FB, 15.9 in NB, 15.0 in AA, 15.8 in TM, 15.5 in TI, and 17.2 in SS. TM, TI, and SS patients often have white blood cell counts which are higher than those in normal individuals. As a result, the number of MNC/ml of blood obtained by Ficoll-hypaque centrifugation is higher from hemoglobinopathy blood than from normal blood. Therefore, growth of BFU-E is reported as the number of colonies/ml of blood in an attempt to provide a physiologic comparison. On day 13, FB and NB colonies were similar in number and the most numerous (means = 2354 and 2384). TM, TI, and SS were similar to each other (means = 672, 852, and 426, respectively, $p > 0.05$), and significantly more numerous than AA colonies (mean for AA = 271; TM vs AA, $p = 0.0006$; TI vs AA, $p = 0.003$; SS vs AA, $p = 0.024$). When *maximal* colonies/ml were compared, differences in growth potential of the various types of erythroid progenitors were most apparent. In all categories, the mean number of colonies/ml increased compared with day 13. FB and NB colonies were similar in number and most numerous (means = 4089 and 3779). TM, TI, and SS were similar in number (means = 672, 852, 426) and were all significantly more numerous than AA colonies (mean for AA = 336, $p < 0.01$ for AA vs TM, TI, and SS). Hemin increased colony numbers in all cultures, with maximal effect at 100 μM in 14/17 AA, 8/10 TM, 4/4 TI, and 200 μM in 7/10 SS cultures.

Thus, TM, TI, and AA BFU-E had similar Ep requirements, and

Erythropoiesis in Hemoglobinopathies *(continued)*

were less sensitive to Ep than FB, NB, or SS colonies. Maximal growth was by day 16 in TM, TI, and AA cultures, but was earlier in FB and later in SS cultures. TM, TI, and SS BFU-E were similar in number and more numerous than AA BFU-E. FB and NB BFU-E were the most numerous.

We conclude that TM and TI BFU-E are similar to each other but different from FB, NB, AA, and SS BFU-E.

Nasal Spray Desmopressin (DDAVP): A Simple Technique for Treatment of Mild Hemophilia A and von Willebrand Disease. Esther H Rose and Louis M Aledort, Division of Hematology, MSMC Box 1006.

The use of plasma products to treat patients with von Willebrand disease (vWD) and Hemophilia A has led to transfusion transmitted diseases. The introduction of DDAVP to the U.S. in 1983 has obviated the need for plasma products for many of these patients. Currently, DDAVP is administered by intravenous (IV) and subcutaneous (SC) routes. These typically give 3- to 5-fold rises of Factor VIII activity (FVIII:C), von Willebrand Antigen (vWAg) and Ristocetin cofactor (vWF) and can correct the bleeding time (BT). A simple atomizer capable of delivering 150 mg per nasal spray can now be used to administer a 300 mg dose to an adult intranasally (IN), which has a bioavailability equivalent to an IV dose of 0.2 mg/kg.

We have treated 22 patients—11 with vWD, 8 mild hemophiliacs, and 3 symptomatic hemophilia carriers—and compared their responses to the nasal spray with those to IV infusion. In vWD, the BT corrected in 62% of patients with either method. The table shows mean results ± standard deviation for patients tested when not bleeding. P values are shown for comparisons of factor levels pre and post treatment for a particular method of administration

Intravenous

Factor	Pre	Post	P
von Willebrand patients:			
FVIII:C%	39 ± 18	143 ± 51	0.0004
vWF%	64 ± 47	143 ± 116	0.005
vWAg%	46 ± 31	133 ± 58	0.0006
Hemophilia A & hemophilia carriers:			
FVIII:C%	16 ± 12	72 ± 33	0.001

Intranasal

Factor	Pre	Post	P
von Willebrand patients:			
FVIII:C%	45 ± 22	115 ± 59	0.002
vWF%	30 ± 29	77 ± 61	0.002
vWAg%	39 ± 35	94 ± 91	0.031
Hemophilia A & hemophilia carriers:			
FVIII:C%	17 ± 11	50 ± 28	0.006

Although the IV method gave somewhat higher factor levels than the nasal spray, most patients achieved levels adequate for hemostasis, both for hemarthrosis as well as for surgical hemostasis.

Clinical efficacy (bleeding episodes or surgical procedures) of the nasal spray was observed in 5 vWD patients, 2 hemophiliacs and 2 hemophilia carriers. Nasal spray DDAVP is a significant advance in the management of these diseases and can eliminate the need for parenteral administration.

Cloning of HIV Insertion Sites in T Lymphocytes by Enzymatic DNA Amplification. Laura Levinson, Chih-Li Kiang, Ari Melnick, Kirk Sperber, Luis Isola, and Carolyn Wasserheit, Mount Sinai School of Medicine, Department of Medicine, Division of Hematology, Box 1079, One Gustave L. Levy Place, NY, NY 10029.

Retroviruses, such as the human immunodeficiency virus (HIV), insert themselves into and become a part of the human genome. It is believed that "integrase," an enzyme that is coded for in the 3′ end of the viral *pol* gene, is responsible for integration. Whether specific sequences serve as insertion sites and what role they play is still unknown.

Our goal is to clone and sequence insertion sites of HIV in human T-lymphocytes to determine whether a specific region of DNA may be a target for retroviral integration. Studying insertion sites by cloning and screening genomic libraries would be too labor intensive. We used a modification of the polymerase chain reaction to study and clone some such sites. Inverse PCR (IPCR) uses two primers constructed to anneal to a known sequence and direct amplification outwards toward the flanking regions. These regions are artificially joined by self-ligation to allow the reaction to proceed in a geometric fashion. The pNY-5′ plasmid is an HIV clone containing the 5′ LTR of the virus and a flanking region of the CEM+ lymphocytes from which the plasmid was cloned. A pNY-5′ *Bam* HI and *Hind*III fragment of 1 kb spans the LTR and a small portion of the flanking DNA. The fragment was blunt ended and circularized. We diluted the self-ligated fragment in CEM− DNA to one copy per cell. IPCR was performed on the ligated diluted material using two primers which anneal to the 5′ and 3′ ends of the 5′ LTR region directing polymerase extension into the flank. The reaction was analyzed by agarose gel electrophoresis which displayed a 400 bp fragment. This fragment was then phosphorylated, subcloned and sequenced. The sequence obtained began at the 3′ primer and read 286bp into the amplified DNA. Homologies were found between the putative flanking regions obtained by IPCR and the IL1 and IL2 receptor genes. We subsequently digested HIV+ CEM cells and the HIV clone, pBH10, with several restriction enzymes. A Southern blot probed with pBH10 DNA identified bands other than those internal to HIV. Those bands, containing flanking DNA, were size selected and subjected to IPCR. The amplification products were similarly cloned and sequenced obtaining a fragment of approximately 300bp. The sequence revealed homology to several human genes and to our original IPCR fragment.

These studies may elucidate the existence of preferential sites for HIV integration and also clarify the heterogeneous manifestations of HIV infection. This knowledge may help devise new therapeutic interventions aimed at interfering with retroviral insertion.

Von Willebrand Factor Binding Protein Extracted from Human Vascular Subendothelium Is Type VI Collagen. Jacob H Rand, Nayana D Patel, Elaine Schwartz, Sheng-li Zhou, Barry J Potter, Department of Medicine, Divisions of Hematology and Hepatology, and Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

We have previously shown that von Willebrand factor (vWF), a glycoprotein which plays a critical role in the adhesion of platelets to injured blood vessels, is present within vascular subendothelium. We, therefore, investigated the identity of the subendothelium binding site (s) for vWF in the following manner.

Methods: Subendothelium was extracted from fresh, mechanically deendothelialized umbilical veins with 2% SDS and 8M urea. The extract was run on SDS 5–10% gradient PAGE and a band at 150 kD which had been shown by radioligand blotting assay to bind ^{125}I-vWF was electroeluted. Homogeneity of the preparation was checked by silver stained SDS PAGE.

Results: This protein had an amino-acid composition similar to that of the type VI collagen alpha-1/alpha-2 chains, was recognized by specific polyclonal antibodies against type VI collagen, and had a similar acidic isoelectric point. Furthermore, we found that purified type VI collagen also bound vWF.

Conclusions: Thus, we have identified the extracted 150kD vWF binding proteins as type VI collagen. This protein may play a significant role in the binding of vWF to vascular subendothelium in vivo.

Infectious Diseases

Nosocomial Bloodstream Infections in Intensive Care Units: Analysis of 167 Cases 1985–1987. Meryl H Mendelson, Burt R Meyers, Cynthia Bournazos, Deborah Danzig, Lavonia Francis, and Shalom Z Hirschman, Division of Infectious Diseases (Box 1090), Infection Control (Box 1152), Mount Sinai Medical Center.

From 7/85–6/87, 167 episodes (E) (191 pathogens, P) of nosocomial bloodstream infections occurred in adult patients in intensive care units at an 1100 bed teaching center (no. E): Medical (49), Surgical (75), Cardiothoracic Surgical (Card Surg), 36, Cardiac (7). The distribution of P groups (%) was gm-pos (47.1), gm-neg (43.9) fungi (6.3), anaerobes (2.6); polymicrobial (11.9). The most prevalent P (%) were S. aureus (SAR, 17.3), Enterococcus (ETC, 13.6), P. aeruginosa (PSA, 12.6), S. epidermidis (SEP, 11.5), Enterobacter (ENB, 7.3), Klebsiella (KLB, 7.3), Candida (CAN, 6.3), Serratia (SER, 5.8), E. coli (ECO, 5.2), Streptococci (STP, 4.2), Bacteroides (2.6), Acinetobacter (ACB, 2.1). Analysis of P distribution for selected ICUs and sources (intravascular, IVASC; respiratory, RESP TR) were:

Medical	Surgical	Card Surg	IVASC	Resp TR
ETC 16.7	PSA 18.8	SEP 25.0	SAR 21.7	KLB 23.1
SAR 13.3	SAR 15.2	SAR 20.0	SEP 21.7	PSA 23.1
SEP 13.3	ETC 12.4	ETC 12.5	CAN 13.0	SAR 15.4
PSA 11.7	ENB 11.8	ECO 10.0	ETC 8.7	SER 15.4
			ACB 8.7	

S. aureus, Enterococci and P. aeruginosa consistently were the predominant pathogens over the 2 year study period.

Liver

Cold Ischemia Induced Bleb Formation: A Potential Cause of Liver Graft Failure. D Sorrentino, K Van Ness, I Ribeiro, CM Miller, Depts. of Medicine (Div. Liver Diseases) and Surgery (Transplant Unit), Mount Sinai School of Medicine, New York, NY.

It has been proposed that cold ischemia-induced liver damage mainly reflects sinusoidal endothelial cell injury, the prevention of which would account for cytoprotection by the University of Wisconsin solution (UW) (Transpl. 46:178). However, although hepatocyte function is not affected by cold exposure (Hepatol. 10:626), hepatocellular ATP content appears to be closely related to the transplantation success rate (Hepatol. 8:471).

To further examine this issue we measured ATP content and ATP regenerating capacity and bleb formation in isolated rat hepatocytes stored for 24 and 48h in Hanks' Hepes (HH) or UW at 4°C. ATP was measured by luminometry, bleb formation by light microscopy and cell size by electronic particle sizing. On day zero ATP (nmoles/10^6 cells, $\bar{x} \pm$ SEM) averaged 7.7 ± 0.5. After 24h ATP was significantly decreased in HH (3.2 ± 0.5) but not in UW stored cells (6.5 ± 0.8). After 48h ATP was significantly decreased in both groups: 1.3 ± 0.4 and 3.8 ± 1.0 for HH and UW, respectively. As in freshly prepared cells, upon rewarming (5, 15, and 30 min at 37°C) ATP content rose by 25 ± 6%, 82 ± 25%, 43 ± 10% in 24h and by 30 ± 7%, 52 ± 5% and 90 ± 24% in 48h UW stored hepatocytes. By contrast, HH stored hepatocytes were incapable of regenerating ATP upon rewarming. An average of 1.5 ± 0.2% of cells displayed blebs when freshly prepared. After 24 hours, blebs were present in 74 ± 7% and 25 ± 3% of hepatocytes stored in HH and UW. In the same groups the number of bleb bearing cells rose to 95 ± 1% and 36 ± 5% after 48 hours. Substantial blebbing (>50% 24h value) appeared earlier in HH (6h) than in UW stored cells (10h). Furthermore, blebs were larger in HH than in UW stored cells after both 24 and 48h (diameter in μ): 24h: 4.4 ± 0.2 (HH) vs 2.2 ± 0.1 (UW); 48h: 6.2 ± 0.7 (HH) vs 2.3 ± 0.1 (UW). Finally, tissue sections of livers preserved in HH but not in UW for both 24 and 48h revealed the presence of extensive amounts of shed blebs in the sinusoidal lumen and loss of endothelial elements.

Conclusions. In isolated hepatocytes, cold ischemia greatly decreases ATP content and ATP regenerating capacity and promotes early and extensive bleb formation. Storage in UW appears to counteract these deleterious effects. In vivo shedding of membrane blebs may cause microcirculatory disturbances leading to graft failure and may potentially explain the correlation between hepatic ATP and liver transplantation success rate. Sinusoidal cell damage or detachment may not be the sole and primary cause of cold ischemia-induced graft failure.

Adipocyte Differentiation in 3T3-L1 Fibroblasts Is Associated with Expression of a Plasma Membrane Fatty Acid Binding Protein. Sheng-Li Zhou, Dario Sorrentino, Decherd Stump, Barry Potter and Paul D Berk, Departments of Medicine (Div. of Liver Diseases) & Biochemistry, Mount Sinai School of Medicine, New York, NY 10029.

In recent studies (reviewed in [1]) we have (i) demonstrated that FFA uptake kinetics are consistent with a facilitated transport process and (ii) identified a 43 kDa plasma membrane FFA binding protein (FABP_{pm}) in rat hepatocytes, adipocytes, cardiac myocytes and jejunal enterocytes. Antibodies to FABP_{pm} selectively inhibit FFA uptake in these cell types. FABP_{pm} is related to the mitochondrial isoform of the enzyme glutamic-oxaloacetic transaminase (mGOT), but not to the family of 14 kDa cytosolic FABPs (2). The 3T3-L1 cell line, of mouse fibroblast origin, retains a typical spindle-shaped morphology when maintained in an exponential growth phase. When grown to confluence, it expresses several enzymes involved in lipid metabolism (3) and differentiates to an adipocyte morphology: within 10 days cells fill with multiple lipid droplets; by 20 days these coalesce into a single, large droplet displacing the nucleus to the periphery.

We have examined the uptake of $[^3H]$-oleate by 3T3-L1 cells, using a rapid filtration technique. In incubations containing 400 μM oleate:bovine serum albumin (1:1), uptake by 3T3-L1 fibroblasts was slow (<15 pmol/min/50,000 cells) and non-saturable. Under the same conditions, uptake by cells in the adipocyte phase was consistently faster (>100 pmol/min/50,000 cells) and displayed kinetic features such as saturability consistent with facilitated transport. A monospecific rabbit anti-rat FABP_{pm}, shown to cross react with mouse liver FABP_{pm} by immunohistochemical methods, selectively inhibited FFA uptake by 3T3-L1 adipocytes, while having no effect on FFA uptake by cells in the fibroblast stage. By immunodiffusion, FABP_{pm} was detected in adipocyte plasma membrane extracts at dilutions of ≤ 1.8, but was undetectable in fibroblast plasma membrane extracts.

Conclusions: Adipocyte differentiation in 3T3-L1 cells involves development of a facilitated plasma membrane FFA uptake mechanism and simultaneous expression of a plasma membrane fatty acid binding protein. These data support our hypothesis that FABP_{pm} plays an important role in facilitated, transmembrane fatty acid transport.

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Hepatic Iron Homeostasis in the Belgrade Rat. BJ Potter, LA Loney, PA Slott, Department of Medicine (Division of Liver Disease), Mount Sinai School of Medicine, New York, NY 10029.

Hepatic transfusional iron overload (TIO) is one of the complications that follows treatment of Cooley's anemia. One of the potential animal

Hepatic Iron Homeostasis in the Belgrade Rat *(continued)*

models for Cooley's anemia is the Belgrade rat, which suffers from a hypohromic, microcytic anemia, inherited as an autosomal recessive trait (b/b). Although the liver is a major site of iron storage, hepatic iron homeostasis has not yet been characterized in this animal. It was therefore the overall aim of this project to examine iron disposition in the livers of both homozygous and heterozygous Belgrade rats with a view to using these animals as models of TIO. In this initial study, iron deposition in the liver has been examined histochemically and compared to kinetic data obtained from the uptake of transferrin-bound iron by isolated hepatocytes. Sprague-Dawley (S-D) rats were also studied as normal controls.

For the histochemical studies, animals were subjected to i.p. injections of iron dextran to simulate TIO. Livers were excised 7 days after the last injection, sectioned and stained by iron. Serum iron parameters were also measured to confirm the iron status of the rats. All livers showed heavy iron deposition in the Kupffer cells, with lesser amounts in the hepatocytes (principally pericentral, as opposed to periportal in S-D rats), and in the portal tracts. In males, deposition was lowest in the homozygotes (b/b) and greatest in the livers of S-D rats. However, livers from female b/b rats contained as much iron as male S-D rats and the female heterozygotes (b/+) contained the heaviest iron deposits. These hepatic iron stores could readily be mobilized by desferrioxamine in b/b animals.

Iron uptake from transferrin by freshly isolated hepatocytes was significantly lower in all the untreated Belgrade rats studied, as compared to the S-D controls. For females, the rates were 1.24 ng and 0.94 ng/10^7 cells/hr for b/+ and b/b hepatocytes respectively, compared to 5.63 ng/10^7 cells/hr for S-D cells ($p < 0.001$). Similarly, in male b/+ hepatocytes the uptake rate was only 0.94 ng.hr as compared to 4.26 ng/10^7 cells/hr for S-D rats. Iron loading of female b/+ rats resulted in a dramatic increased in iron uptake to 12.68 ng Fe/10^7 cell/hr for the first hour, which then leveled off to almost normal values.

These preliminary results suggest that the Belgrade rat has considerable potential as a model for studying hepatic iron homeostasis and liver transfusional iron overload seen in Cooley's anemia.

Nephrology

NaK2Cl Cotransport in the Mouse Medullary Thick Ascending Limb (mTAL) Cells. Deepak Kaji, Renal Section, Room 9A17, Department of Medicine, VA Medical Center, Bronx, NY 10468.

The majority of Na transport at the luminal surface of the thick ascending limb cell is mediated by NaK2Cl cotransport pathway. We evaluated the NaK2Cl cotransport in monolayers of mouse mTAL cell by measuring the K influx with ^{86}Rb in media with 145 mM NaCl and 5 mM KCl. K influx was linear for at least 5 minutes with or without bumetanide. Bumetanide inhibited K influx with 50% inhibition at 0.8 μM. The difference in K influx without and with 10 μM bumetanide was taken as a measure of NaK2Cl cotransport. The NaK2Cl cotransport was not different whether defined by the K influx inhibited by removal of external Cl, by removal of external Na or by the addition of bumetanide. The dependence of bumetanide sensitive (BS) K transport on external Na and K was saturable with Michaelis Menten kinetics and apparent $K_{0.5}$ of 14 and 2.8 mM respectively, similar to that found in other cell types. The BS K transport exhibited a linear dependence on Cl. The BS K influx was inhibited in acid media; at a pH of 7.2, BS K influx was diminished 32%. Angiotensin (10 nM) had no effect on BS K influx. Atrial natriuretic peptide (100 nM) was also without effect on the BS K influx. However, isoproterenol (10 μM), a beta adrenergic agonist that increases adenylate cyclase, stimulated BS K transport by 35%. An increase in medium osmolarity to 450 mosm/kg stimulated NaK2Cl cotransport by 40%. Epidermal growth factor (10 nM) also increased BS K transport by 35%.

These results suggest that the cultured mouse mTAL cells may provide a good model for the study of NaK2Cl cotransport and the factors affecting that transport pathway in the mTAL cells.

The Use of Functional Imaging to Simultaneously Measure Glomerular Filtration Rate (GFR) and Renal Plasma Flow (RPF), or Effective Renal Plasma Flow (ERPF) and Renal Plasma Flow. S Kupfer, P Stritzke, P Zhu, SJ Goldsmith, S Vallabhajosula, and L Burrows, Division of Nephrology of the Department of Medicine, and the Departments of Radiology and Surgery, Mount Sinai School of Medicine, Box 1027, New York, NY 10029.

We have devised a noninvasive method, using gamma camera scintigraphy, to measure GFR and RPF simultaneously with ^{99m}Tc-DTPA, or ERPF and RPF with ^{123}I-hippuran. The data are recorded in two minutes. Radionuclide is injected IV and the time activity response over the cardiac or aortic, and renal regions of interest are recorded. Venous blood is sampled at a known time after injection and the plasma is counted in a well counter. Gamma camera and well counter are calibrated so that all quantitative measurements of radioactivity are converted into absolute values. Deconvolution of the cardiac or aortic (input) and renal (output) time activity curves by orthogonal polynomials (DOP method, Stritzke et al, IEEE Trans Med Imag, 1990) provides a linear response function (LRF) of the kidney vs time. LRF is expressed in units of flow. The peak value of the LRF is equivalent to RPF, while the plateau value is a measure of GFR or ERPF depending on the isotope used. Values can be calculated in each pixel and functional images of RPF, GFR, and ERPF can be computer generated and photographed.

To date, we have evaluated these values with concurrent measurements of exogenous creatinine, inulin and PAH clearances in two dogs and with endogenous creatinine clearances in two patients following renal transplantation. The results obtained by the DOP method compare favorably with those obtained by classical clearance methodology.

	$C_{cr}/C_{in}/C_{DPTA}$	C_{pah}	GFR_{DOP}	RPF_{DOP}	$ERPF_{DOP}$
	mL/min				
Dogs 3 DPTA 1 Hippuran TOTAL 4	67–104	155–269	83–108	340–493	168
Patient 1 4/6 acute reject Tx	16	(^{99m}Tc–DTPA)	8.5	40	
5/30 improved	36	(^{99m}Tc–DTPA)	39	210	
Patient 2 2½ yrs. post Tx	107	(^{99m}Tc–DTPA)	103	400	

Early Indicators of Renal Disease in Parenteral Substance Abusers (SA). Dubrow A, Wadhwani S, Klein P, Levin NW, Division of Nephrology and Hypertension, Beth Israel Medical Center, New York, NY 10003.

Parenteral abuse of narcotics, particularly of heroin, has been associated with a specific renal lesion, focal and segmental glomerular sclerosis (FSGS). Manifest clinically as nephrotic syndrome, hypertension, and azotemia, FSGS progresses rapidly to ESRD. The etiology of this lesion remains obscure.

In an attempt to identify a subpopulation of SA at risk for ESRD, we retrospectively examined the charts of 249 randomly selected healthy SA voluntarily admitted for detoxification between 1/89 and 12/89. Indicators of renal disease were azotemia (BUN $>$ 20 mg/dl or creatinine $>$ 1.4 mg/dl, hematuria ($>$3 RBC/HPF), or proteinuria ($>$1+ albumin on dipstick). Alcohol abusers without other SA served as one control group. Twelve patients abusing marijuana, benzodiazepines or tricyclic antidepressants served as a second control population. Seventeen of sixty-seven heroin abusers (25%), seventeen of one hundred and forty-five cocaine, non-heroin abusers (12%), and four of twenty-five alcohol abusers (16%) had renal abnormalities. None of the twelve abusers of other substances had abnormalities. We found an overall incidence of renal abnormalities of 14%. Patients who are male, black, and abusers of heroin appear to be at greatest risk for renal lesions ($p = .05$).

We believe that these data warrant a prospective examination of parenteral SA of all etiologies. We will be able to isolate heroin abusers from abusers of other parenteral agents in order to further study renal lesions. Evaluation early in the course of SA associated renal lesions could provide insight into the pathogenesis of FSGS and other renal diseases in these patients and possibly into methods of therapeutic intervention.

Nuclear Medicine

A New Radiopharmaceutical for the Treatment of Rheumatoid Arthritis. M Chinol, S Vallabhajosula, MJ Klein, RE Gordon, SJ Goldsmith.

Intra-articular injection of radioactivity into an inflamed joint (Radiation Synovectomy), has been extensively used in Europe for more than 25 years as an alternative to surgical intervention. We have developed a new radiopharmaceutical, ^{166}Ho-FHMA, using a radionuclide, Holmium-166 (Ho-166) with a short half-life ($t_{1/2} = 27$ hrs) and ideal beta emission for optimal tissue penetration. We have attached Ho-166 to a particulate, biodegradable carrier: macroaggregates of ferric hydroxide (FHMA). The safety of the radiopharmaceuticals was first studied in normal rabbits (N = 4). Subsequently, we have evaluated safety and efficacy in a rabbit model of arthritis (antigen induced arthritis, AIA, N = 11) which histologically resembles rheumatoid arthritis in man. The radiopharmaceutical was injected into the knees (0.5 mCi/Kg) and the total extra-articular leakage of Ho-166 was found only 0.05% of the injected dose within 2 days.

To determine the efficacy, 5 animals were sacrificed 4–5 days postinjection, 3 at 7 days and 3 at 14 days. The treated knees (TK) and the control knees (CK) were removed and prepared for histological evaluation. 5 criteria, acute (AI) and chronic (CI) inflammation, synovial proliferation (SP), fibrosis (F) and cartilage changes (CC), graded from 0 to 4, were used by two pathologists to study the efficacy of the treatment.

	4–5 days		7–14 days	
	CK	TK	CK	TK
AI	1.8 ± 0.8	2.2 ± 0.8	2.0 ± 0.6	1.1 ± 0.9
CI	2.0 ± 0.7	2.0 ± 0.7	2.7 ± 0.9	1.6 ± 0.8
SP	1.8 ± 0.8	1.2 ± 0.4	1.8 ± 0.7	1.1 ± 0.7
F	2.2 ± 0.4	2.4 ± 0.5	2.8 ± 0.4	2.0 ± 0.6
CC	1.0 ± 0	0.8 ± 0.4	1.2 ± 0.7	0.2 ± 0.4

No differences were observed at 4–5 days between TK and CK ($p \geqslant 0.1$). At 7–14 days, instead, the TK showed a marked improvement especially with respect to AI and CI inflammation ($p \leqslant 0.01$). These results suggest that a single intra-articular injection of ^{166}Ho-FHMA may be safe and effective for the treatment of synovitis.

Pulmonary Medicine

Assessing Drug Resistance among Tuberculosis Patients in New York City. JJ Adler, Pulmonary Division, Toni Davis, S Schultz, New York City Department of Health, New York, NY.

The prevalence of citywide tuberculosis (TB) drug resistance is difficult to assess. Because of the large number of laboratories (labs) which perform drug sensitivity studies, the difference in technologies used, and the patient selection process, there is no number which can be reliably used to obtain prevalence of resistant patients.

In order to better evaluate drug resistance information and to establish a standardized approach to sensitivity testing, the New York City Department of Health (DOH) sent a letter and questionnaire to 56 directors of labs in the city requesting information on TB drug testing in mycobacteriology labs. Responses were received from 48 labs. Preliminary data indicates an average resistance rate of between 10–20% of specimens processed. Of those 28 labs which tested all *M.tb.* cultures for drug sensitivity, 12 hospital labs performed 2,900 tests annually with a resistance rate of between 0–70%, and 16 referral labs performed 1,023 tests with a resistance rate of between 0–33%.

The number of specimens tested and those that were positive for *M.tb.* are as follows:

Testing Lab	No. Specimens	%M.tb
Hospital (12)	76,292	4.9
DOH Referral (11)	31,231	3.5
Other Referral (5)	6,140	1.1

Additional questionnaires have been sent to obtain more specific patient information and updated data will be presented regarding the wide range of drug resistance noted above.

Erythromycin Inhibits Airway Smooth Muscle Response to Carbachol. EN Schachter, E Zuskin, S Goswami, F Celikoglu, J Bonheur, N Rienzi, S Maayani, Z Marom, Mount Sinai Medical Center, New York, NY 10029.

The role of antibiotics in obstructive airway disease, other than for the management of susceptible infections, remains undefined. In previous studies (ARRD in press) we have demonstrated that erythromycin inhibits respiratory glycoconjugate release from human airways and that this release is calcium dependent. The present investigation was undertaken to study erythromycin's possible role in the airway's response to carbachol.

Hartley male guinea pigs were pretreated for 18 hours with erythromycin lactobionate (E) Ampicillin (A) or the control vehicle (V) administered intraperitoneally every 6 hours prior to sacrifice. We measured the isometric tension developed in the excised guinea pig tracheal (GPT) rings suspended in an organ bath containing 20 ml of Krebs Buffer at 37C. Eight GP's were used for each treatment and GPT's were divided into 4 rings each for replicate experiments. Concentration response curves to carbachol (C) were obtained by serially adding C in concentrations from 10^{-8} to 3×10^{-5} M. Concentration response curves were computer fitted to a logistic equation and response parameters were derived (Emax, EC50 and slope:

Concentration Response Parameters of C in Treated GP's

	Emax (gms)	EC50 (M)	Slope
Erythromycin	2.40	6.25×10^{-5}	0.76
Control	3.63	6.37×10^{-5}	0.67
Ampicillin	2.26	6.2×10^{-5}	0.84
Control	2.52	3.8×10^{-5}	0.86

A significant difference ($p < 0.05$) was demonstrated for Emax between E and V treated GPs but not between A and V treated animals.

Erythromycin Inhibits Airway Smooth Muscle Response to Carbachol (*continued*)

Additionally we studied phasic and tonic responses to C in E and V treated animals. Phasic responses to C in calcium free EGTA medium were prolonged in E treated GPs but not in V treated GPs.

We suggest that erythromycin reduced carbachol induced contraction in GPT. The changes seen in phasic and tonic responses suggest a calcium mediated mechanism.

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Analysis of the Forced Expiratory Spirogram by Computation of the Distribution Function of Expiratory Rate-Constants. LK Brown, HM Lacker, M Pilipski, A Miller, Division of Pulmonary and Critical Care Medicine, and Departments of Physiology and Biophysics, and Biomathematics, Mount Sinai Medical Center, New York, NY 10029.

Permutt and Menkes (1979) proposed a model in which the forced expiratory spirogram (FES) is analyzed as the summation of a continuum of parallel elements, each discharging its volume with a characteristic time constant (D). They used the first and second moments of the FES to solve for the parameters μ (mean) and σ (standard deviation) that characterize a lognormal distribution of these time constants [h(D)]. However, this required an a priori guess that this distribution was lognormal.

We developed an alternative method in which a function of the form $f(t) = a/(t + r)^k$ is fitted to the FES data, and h(D) computed exactly using the inverse Laplace transform. In normal subjects, this distribution was similar in shape to the lognormal but μ and σ differed significantly. We applied the method to 18 normal subjects and 12 bronchitics, computing μ and σ for the rate constant (1/D) rather than the time constant as μ and σ for the latter were not always defined (the integrals did not converge). Correlations with FEV_1/FVC and forced mid-expiratory time (MET):

(all P < .05)	Normal		Bronchitic	
	μ	σ	μ	σ
FEV_1/FVC	0.86	0.84	0.89	0.74
MET	−0.77	−0.75	−0.78	−0.58

We conclude that μ and σ determined in this way correlate highly with conventional spirometric indices of obstruction and are not subject to errors inherent in assuming a lognormal h(D). Analysis of sensitivity and specificity are in progress.

Mucus Stimulatory Factor Is Secreted by a Human Macrophage Hybridoma Cell Line. E Gollub, S Goswami, K Sperber, L Mayer, Z Marom, Mount Sinai Medical Center, Division of Pulmonary and Critical Care Medicine and Division of Clinical Immunology and Allergy, New York, NY 10029.

A macrophage and monocyte-derived oligopeptide (MMS) which induces mucus production in vitro in human airway explants and secretory epithelial cells has previously been described. In recent studies on the secretagogue, our laboratory has utilized a human macrophage hybridoma cell line (HB-63) which offers a more readily available source of cells. These cells upon stimulation with LPS were found to secrete into the media not only a low molecular weight oligopeptide similar to MMS, but a high molecular weight protein (68,000 D) as well, which induced mucus secretion in human airways and epithelial by an invitro assay system. The 68 KD protein was detected by SDS-page and shown by Western blot analysis to cross-react with the antibody that had been generated against the oligopeptide. The present study describes the partial purification and characterization of the 68 KD protein from both lung macrophages and hybridoma HB-63.

Purification of the 68 KD protein involved ultrafiltration of the conditioned media after induction with LPS or zymosan, passage through a Sepharose blue column to remove traces of BSA which might be present from the media, and then passage through a sephadex G-50 column. Void volume fractions were tested by an immunodot-blot assay and positive fractions were combined and used for the in-vitro bioassay to assess mucus glycoprotein (MGP) secretion. Immunoblot-positive fractions always showed dose-dependent biological activity. Amino acid analysis of the 68 KD proteins from both sources indicated they are acidic proteins and are very similar in amino acid composition. The relationship, if any of the 68 KD protein to the 2KD oligopeptide (MMS) is not yet clear.

In summary, we have shown that both macrophages and the hybridoma cell line HB-63 can be stimulated to secrete novel proteins which may play important roles in the regulation of mucus secretion.

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Research Day in Medicine 1990

Part 2: Abstracts by Students, Fellows, and House Staff

Biomathematics

Maintenance Oral Sulfasalazine (ASA) Prolongs Remission in Ulcerative Proctitis (P) and Proctosigmoiditis (PS). D LaRosa, P Rubin, C Bodian, D Present, Department of Medicine and Department of Biomathematical Sciences, Mount Sinai Medical Center, New York, NY.

Several oral and topical regimens have proved effective in inducing clinical remission in patients with P and PS, but there are little data on their role in maintenance of remission in these localized diseases. A retrospective study of 206 patients with P (115) and PS (91) was undertaken to determine whether the duration of clinical remission was influenced by a) initial therapy or b) maintenance therapy with oral ASA. The patients were analyzed by age, sex, sigmoidoscopic activity (1−4+), and whether first or recurrent attack. Effective induction therapy was defined as disappearance of diarrhea, urgency, gross blood, and mucus within 28 days of treatment. Initial therapy was classified according to the 5 regimens utilized to induce remission: topical steroids (50), topical ASA (20), oral ASA (33), oral and topical ASA (18), or oral ASA and topical steroids (85). Followup data were available on 160 patients who achieved remission on one of these regimens; these patients were classified by their maintenance therapy as either oral ASA (83) or none (77). Relapse rates were plotted against time (median followup = 32 mos) and analyzed by methods for censored followup data.

Results: Clinical remission within 28 days was achieved in 97 of the 206 patients (47.1%) by one of the 5 induction regimens. Logistic regression analysis showed no significant differences among the 5 regimens in inducing remission within 28 days. Ultimately 194 of the 206 achieved remission (94.3%). After remission had been achieved in these 194 patients, relapse was documented in 160. The relative risk of clinical recurrence was not influenced by initial extent of disease (P vs

PS), age, sex, severity of inflammation or first versus recurrent episode. Although total relapse rates were similar in the 2 maintenance groups, the median interval for relapse was significantly longer for the patients maintained on ASA (9 mos) when compared to no treatment (6 mos) with $p = 0.02$.

Conclusion: The data suggest that oral ASA sustains remission in P and PS and may be effective as maintenance therapy.

Cardiology

Ventricular Pacing Is Effective Therapy for Carotid Sinus Hypersensitivity. Jay Curwin, Steven L Winters, Jorge Camunas, Manuel Estioko, Unsoon Shagong, J Anthony Gomes, Division of Cardiology, Box 1030, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY.

The preferred mode of cardiac pacing in patients with carotid sinus hypersensitivity (CSH) of the cardioinhibitory type is unclear. Thus, we followed 26 consecutive patients (mean age 73 ± 10 years) with CSH for 30 ± 26 (range 1–100) months after ventricular demand (VVI) or dual chamber (DDD) pacemaker implantation. All patients had experienced recurrent syncope prior to pacemaker insertion for a mean of 3 ± 2 episodes. Patients were evaluated for toleration of ventricular pacing at the time of implantation, and the five who had hypotensive responses received DDD units. At follow-up, 1 of 9 (11%) VVI patients and 2 of 17 (12%) DDD patients had recurrent syncope ($p =$ ns). One patient who had received a VVI pacemaker developed manifestations of the pacemaker syndrome.

Thus, in the absence of documented vasodepressor responses to pacing at the time of pacemaker insertion, the recurrence rate of syncope from CSH is low regardless of whether ventricular demand or atrioventricular synchronous pacing systems are used.

Transesophageal Echo Is Superior to Transthoracic Echo for Detection of "Smoke." Edward A Fisher, Jeffrey A Stahl, Jacqueline H Budd, Richard A Goldman, Richard L Taikowski, Allan S Klapper, Young Lee, Martin E Goldman, Mount Sinai School of Medicine, Division of Cardiology, New York, NY 10029.

The presence of "smoke" in dilated cardiac chambers, seen with 2-D echo, may portend thrombus formation. Transesophageal echo (TEE), which images at a higher frequency with less attenuation than transthoracic echo (TTE) due to its proximity to the heart, may be superior for smoke detection.

To determine the incidence of smoke, TEE was performed immediately after standard TTE in 200 nonsurgical patients. Smoke was seen in 58 chambers in 47 patients: left atrium/appendage (LA/A) (32 cases, 16%), right atrium (8, 4%), left ventricle (7, 3.5%), aorta (7, 3.5%), right ventricle (2, 1%), pulmonary artery (1, 0.5%), pulmonary vein (1, 0.5%). But only 8/58 cases of smoke were seen by TTE. We compared the 32 pts with LA/A smoke to those without smoke.

	#	AFib	LA thrombus	dilated LA
+ Smoke	32	17	5	28
− Smoke	168	15*	6**	83*

$^{*}p = .0001$, $^{**}p < .01$

Thus, TEE is more sensitive than TTE for detection of cardiac smoke. Also, atrial fibrillation (AFib), large atria and smoke may constitute a dangerous triad promoting thrombus formation.

Detection of Aortic Disease by Transesophageal Echo Identifies Patients at Risk of Stroke. Edward A Fisher, Jeffrey A Stahl, Jacqueline H Budd, Richard L Taikowski, Richard A Goldman, Allan S Klapper, Jesse Weinberger, Stanley Tuhrim, Deborah R Horowitz, Martin E Goldman, Mount Sinai School of Medicine, Division of Cardiology, One Gustave L. Levy Place, New York, NY 10029.

Transesophageal echocardiography (TEE) can rapidly and accurately evaluate the aortic root and ascending, transverse and descending thoracic aorta. To determine the incidence and significance of aortic pathology, we reviewed 200 consecutive nonsurgical TEE studies (patient age 60.4 ± 14 years).

Fifty-two patients (26%) had aortic pathology: abnormal plaque in 42 (descending in 33, ascending in 5, arch in 4), dilation in 14, dissection in 3, abscess in 1. Males had more aortic pathology (32/93, 34%) than females (20/107, 19%) ($p < .02$). Importantly, patients with recent stroke had a greater incidence of aortic pathology (31/76, 41%) than nonstroke patients (21/124, 17%) ($p = .0003$).

Forty patients with documented stroke had both carotid duplex imaging and TEE. Fourteen of 15 patients (93%) with aortic plaque also had carotid disease suggesting that thoracic aortic plaque may be a marker for generalized vascular atherosclerosis.

Thus, TEE aortic imaging may be an important component of the comprehensive evaluation of potential sources of peripheral and central emboli.

Contrast 2-D Transesophageal Echo: The Method of Choice to Detect Patent Foramen Ovale. Jeffrey A Stahl, Edward A Fisher, Jacqueline H Budd, Stanley Tuhrim, Deborah R Horowitz, Martin E Goldman, Richard L Taikowski, Richard A Goldman, Division of Cardiology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1030, New York, NY 10029.

Patent foramen ovale (PFO) demonstrated by contrast transthoracic echo (TTE) is an important risk factor for stroke, reported in up to 40% of young stroke patients. Transesophageal echo (TEE) has better resolution with less attenuation than TTE, and may be more sensitive for PFO detection. To determine the incidence and significance of PFO, we performed peripheral contrast injections during 2-D TTE and TEE color flow Doppler (CFD) in 170 nonsurgical patients (aged 62 ± 15 yrs), 69 with recent stroke. PFO was defined by either microbubbles in the left heart following right-sided injections or as color turbulence from right to left atrium in the absence of another intracardiac shunt.

Nine of 170 (5.3%) patients (mean age 74 yrs, range 49–83) had PFO identified by TEE, while only 2 were seen by CFD or TTE. Importantly, 8/9 PFOs were seen in patients ≥ 60 yrs. The incidence of PFO in stroke patients (7/69, 10%) was greater than in non-stroke patients 2/101, 2%) ($p < .02$). Thus, PFO may be an important risk factor for stroke in patients of all ages. Contrast 2-D TEE should be considered the definitive technique for PFO detection.

Clinical Immunology

Identification of the Receptor for a Novel Human B Cell Differentiation Factor. A Pizzimenti, R Furman, M Cidon, J Barest, L Mayer.●

Abstract published in Fed Proc 1990;4(7): A 2064 (Abstract no. 2150).

Immunoglobulin and T Cell Receptor Gene Transcription Is Regulated by Different Lymphokines in Mast Cell Lines from the Murine Embryo. Edward J Siden, Division of Clinical Immunology, MSMC Box 1089.

We have previously shown that mast cell lines generated by Abelson murine leukemia virus infection of cells from the murine placenta express a spectrum of RNA molecules that might be expected of a lym-

Immunoglobulin and T Cell Receptor Gene Transcription Is Regulated by Different Lymphokines in Mast Cell Lines from the Murine Embryo. (*continued*)

phoid progenitor cell. Although none of the lines show any evidence of immunoglobulin (Ig) or T cell receptor (TcR) protein synthesis or receptor gene segment rearrangement, we did observe transcripts of germline genes of both receptor families. Only Ig heavy chain variable regions were transcribed constitutively, whereas both Ig mu and TcRgamma constant region loci were induced after culture in bromodeoxyuridine (BUdR).

We show here that normal lymphokines can have similar inducing effects as the anti-proliferative drug, BUdR. Even more interestingly, B cell and T cell antigen receptor transcripts are induced by different lymphokines. Germline mu heavy chain transcripts are induced by interleukin 6 and the TcRgamma RNA is induced by interleukin 3. Experiments are currently in progress to determine whether a cell with these lymphoid stem cell-like properties exist in the normal uninfected embryo and whether this cell may be a mast cell.

Endocrinology

The Wistar Thyroid Cell Line Interacts Directly with Wistar Thyroid Reactive T Cell Clones: Direct Evidence for Thyroid Cell Provision of Second Signal. H Kimura, TF Davies, Division of Endocrinology, Mount Sinai School of Medicine, New York, NY 10029.●

Wistar rats are susceptible to the induction of experimental autoimmune thyroiditis and recently a cloned Wistar rat thyroid epithelial cell line (WRT) has become available. In this study we have examined the cloned thyroid cell-T cell interaction in normal Wistar rats by using a unique in vitro model. Normal Wistar lymph node (LN) cells showed an early and vigorous proliferative T cell response to WRT cells (Stimulation Index = 19.4) which was both MHC class I and class II antigen restricted. Such Wistar LN cells were cloned by limiting dilution technique and 7 of 23 (30.4%) T cell clones proliferated in the presence of WRT cells alone and 1 clone required the combination of WRT cells and thymocytes. None of these clones were autoreactive. WRT reactive T cell clones which could be more extensively characterized were CD4+, MHC class II antigen restricted, and secreted rat gamma interferon basally and in response to WRT cell exposure. One clone showed cross-reactivity between WRT cells and purified rat thyroglobulin (Tg) antigen.

These observations demonstrate that thyroid epithelial cells have the capacity to present autoantigens (for example Tg) directly to helper T cells in the absence of all other antigen presenting cells; an interaction relevant to the etiology of autoimmune thyroid disease. Our experiments provide the first evidence that thyroid cells can provide the second signal necessary for successful antigen presentation and the induction of proliferation rather than anergy. Furthermore, this syngeneic system offers important advantages for the further investigation of thyroid-immune interactions and escape from tolerance induction in autoimmune thyroid disease.

Transplants of Migratory GnRH Cells into the Brain Are Capable of Inducing Gonadal Recovery in Hypogonadal (HPG) Mice. I Livne, MJ Gibson, and AJ Silverman, Dept. of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, & Dept. of Anat. Cell Biol., Columbia Univ., New York, NY 10032.

GnRH neurons are derived from the olfactory placode, and migrate into the CNS during embryogenesis. In this study we examined the capability of transplants containing this migratory population of GnRH cells to establish functional connections with the median eminence (ME), and hence to induce gonadal recovery in mutant hpg mice.

Nasal area tissue from normal mouse embryos at E12 or E13 was grafted bilaterally into the anterior hypothalamus or preoptic area of adult hpg males (n = 9). Following survival of 2 to 8 weeks post grafting, the animals were perfused, their testes weight recorded, and the brains processed for GnRH immunocytochemistry. In 4 animals the grafts proliferated across the midline, with some tissue entering the third ventricle. Of these, L28 showed gonadal recovery (testes weight of 23.6 mg, mean weight of untreated hpg testes: 7.5 mg). This recovery corresponded to the presence of a small number of GnRH cells in the graft and a sparse innervation of the ME. L20 had a much more robust ME innervation but due to early sacrifice (20d) gonadal recovery was not yet evident. In those animals where the graft remained wholly within the parenchyma, testicular recovery did not occur. However interesting observations were made. In N31 GnRH cells appeared to migrate out of the graft into the host and these cells elaborated long bifurcating axons, some of which coursed medially in the direction of the third ventricle. In L30 migration of cells into the host was less clear cut, but it also had GnRH axons which grew toward midline and then headed ventrally toward the ME.

These observations suggest that migratory GnRH neurons when grafted into the brain of adult hpg mice retain some migratory potential and can elaborate extensive axonal projections, which upon innervation of the ME can induce gonadal recovery. Supported by NS 90335.

Time-Dependent Changes in the Pulsatile Secretion of LH Following Ovariectomy in Female Mice. Gregory M Miller and Marie J Gibson, Division of Endocrinology, Mount Sinai School of Medicine, NY, NY 10029.

In our first study of plasma LH pulsatility in female mice (Endoc Soc Abstr #920,'89), we detected pulses in all normal females studied 22 days after ovariectomy (ovex) and in 9/13 hypogonadal mice with preoptic area grafts.

To evaluate changes in pulsatility after ovex in normal mice, in the present study we evaluated 9–11 week-old females on day 1, 7 or 22 following ovex. All mice were fitted with intravenous catheters one day before blood sampling. Sequential blood samples were collected from awake, freely-moving mice at 10 min intervals for 4 h during the latter half of the light period (14:10 L/D). Plasma (60–80 μl) was separated and stored (−20 C) for RIA of LH, performed on 25 μl duplicates. Resuspended red blood cells (0.05 ml of 2U heparin/saline) were readministered following the next sample withdrawn.

Group	N	Plasma LH (ng/ml)	# Pulse/h	Pulse Amplitude (ngLH)
Day 1	5	0.33 ± 0.03	0.45 ± 0.20	0.37 ± 0.11
Day 7	6	1.11 ± 0.38	0.87 ± 0.20	1.62 ± 0.47
Day 22	10	1.02 ± 0.15	0.90 ± 0.12	1.06 ± 0.32

LH pulsatility was detectable in 3 of 5 mice on day 1 after ovex and in all other mice tested. Mean plasma LH and pulse amplitude were significantly elevated by day 7 after ovex and remained elevated at day 22. The number of pulses per hour were variable, although tending to increase with time after ovex.

We conclude that the onset of the negative feedback response of elevated LH after removal of ovarian steroids occurs during the first week following ovex. We will further examine changes within the first week to determine the nature of the increase in pulsatility. The present findings of a time-dependent increase in LH pulsatility after ovex are consistent with studies in female rats.

Supported by NIH Grant HD19077.

Detection of Autoantibodies to Recombinant Human Thyroid Peroxidase by Ultrasensitive Enzyme Immunoassay. DL Kendler, A Martin, RP Magnusson, and TF Davies, Departments of Medicine and Pharmacology, Mount Sinai School of Medicine, New York, NY.

Autoantibodies to thyroid peroxidase (TPO), the thyroid "microsomal" antigen, are widely utilized in the diagnosis of human autoimmune thyroid disease. Crude human thyroid preparations of TPO are of differing potency, contain residual thyroglobulin (Tg) and other human membrane antigens, and are available in only limited amounts. Hence, immunoassays for anti-TPO are unstandardized and of variable sensitivity and specificity.

We co-transfected the Chinese hamster ovary (CHO) cell line with a full length human TPO cDNA expression plasmid (Kaufman et al, J. Clin. Invest. 84:394, 1989) and selected a high expressing recombinant TPO positive cell population (CHO-TPO) by Northern blot analysis, then fluorescence laser flow cytometry using both human polyclonal and murine monoclonal anti-TPO antibodies. Solubilized 100,000 × g membrane preparations from both CHO-TPO and CHO cells were used as antigens in a specific ELISA with CHO antigen serving as background control. In a selected series of known anti-TPO positive ($n = 46$) and negative ($n = 73$) sera there was a high correlation between ELISAs utilizing recombinant or natural-TPO antigen ($r = 0.93$). There appeared to be no difference in the affinity of high titer human anti-TPO for recombinant and natural-TPO antigen with both ELISAs able to detect 0.05 U/ml of anti-TPO activity (reference preparation NIBSC 66/387).

These data predict a new era in standardized thyroid autoantibody testing utilizing recombinant antigen preparations.

Human Recombinant Thyroid Stimulating Hormone (TSH) Induces Human Thyroid Cell Growth In Vitro. GK Huber, P Fong, E Conception, and TF Davies, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

We assessed the bioactivity of newly available, partially-purified, human recombinant TSH (hTSH-rec; gift of J. McPherson, Genzyme Corporation) in our recently characterized human fetal thyroid cell system (Endocrinology, 126: 869, 1990). A consistent dose-related accumulation of extracellular cyclic AMP was found with increasing concentrations of hTSH-rec up to a maximum of 3500%. Using human TSH-I-6 and RP-I as standards, the potency of hTSH-rec was estimated to be 5.6 IU/mg providing a fetal thyroid assay sensitivity of >0.25 uU/ml. Human thyroglobulin release was also stimulated by hTSH-rec at concentrations >50 μU/ml. Thyroid cell growth, as assessed by changes in cell number measured by automated cell counting, was markedly induced, also in a dose-dependent manner by hTSH-rec, reaching a plateau at 5 mU/ml with a 4.7 fold increase in cell numbers and reducing the cell doubling time to 31 hours.

In conclusion, human recombinant TSH, which is devoid of contaminating LH and FSH, is a biologically potent preparation as measured in an homologous human system. It will serve as the definitive international standard for future bioassays and immunoassays.

Thyroid Stimulators Induce Growth and Expression of c-fos Oncogene in Human Fetal Thyroid Cells. GK Huber, R Safirstein, and TF Davies, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Human fetal thyroid cells serve as a predictable in vitro model of thyroid cell growth and function allowing the avoidance of the commonly used rat thyroid cell lines (Endocrinology, 126:869, 1990). Using this system, we have shown that TSH or autoantibodies to the TSH receptor derived from Graves' disease patient sera stimulated fetal thyroid cells to increase their growth rate over a 96 hour observation period. This occurred in a dose-dependent manner, up to 300% above baseline, similar to that observed after addition of insulin and TSH. In order to further investigate the underlying mechanisms, we have examined the regulation of the oncogene c-fos in this system. Human fetal thyroid cells were grown in a serum-free medium devoid of insulin and TSH for 5 days. Expression of c-fos was then evaluated by Northern blot analysis of cells exposed to insulin and/or thyroid stimulators. Under basal conditions of slow growth, only a low concentration of c-fos mRNA was expressed. Addition of insulin caused a 2.1-fold increase, TSH a 6.1-fold increase, and together a 9.7-fold increase in c-fos expression after 30 minutes of stimulation. IgGs derived from patients with Graves' disease showed similar c-fos induction.

These data demonstrate that thyroid growth stimulators induce human thyroid cell growth and c-fos oncogene expression in human fetal thyroid cells in a synergistic manner. Furthermore, the induction of c-fos oncogene can be used as important evidence of continuing fetal thyroid cell growth in vitro.

Incidence of Hypoglycemia and Hyperglycemia in Hospitalized Patients: Associated Risk Factors and Mortality. MK Barton, PL Linekin, E Corkery, A Stagnaro-Green, and SH Roman, Division of Endocrinology, Box 1055, Mount Sinai School of Medicine, New York, NY 10029.

There is a paucity of literature regarding hypoglycemia (hypo) and hyperglycemia (hyper) in hospitalized patients. We have prospectively surveyed the incidence of hypo (≤49 mg/dl) and marked hyper (≥400 mg/dl) in hospitalized patients over a 2 month period (5221 admissions). Patients were identified, charts reviewed and hospitalization outcome obtained. The incidence of hypo was 1.7% (106 events in 85 patients) and that of hyper was 2.2% (166 events in 110 patients). A prior diagnosis of diabetes (DM) was present in 27% of patients with hypo and 66% with hyper. Risk factors for hypo included infection (47%), renal disease (32%), liver disease (27%) and septicemia (25%). Risk factors for hyper included infection (61%), inadequate insulin regimen (43%), renal disease (37%) and septicemia (23%). In 17% of hypo episodes and 46% of hyper episodes there were documented DM complications. Spurious hypo secondary to inadequate specimen preservation or lab error occurred in 9% of hypo events, and spurious hyper secondary to specimen withdrawal above intravenous or from broviac lines occurred in 14.5% of hyper events. Mortality rate was 16.5% in hypo patients, 9.1% in hyper patients and 2.4% in the remainder of hospitalized patients during the 2 month period ($X^2 = 106.9$, $p < 0.0001$).

We conclude: 1) Hypo and hyper occur in hospitalized patients with and without a previous diagnosis of DM, 2) Hospitalized DMs with known complications have an increased risk for both hypo and hyper events, 3) Spurious results of hypo and hyper are frequent in hospitalized patients, 4) Hypo and hyper serve as indicators for increased hospital mortality.

Gastroenterology

Peripheral Neuropathy in Crohn's Disease Patients Treated with Metronidazole: Who Develops It? How Long Does It Last? G Khilnani, P Rubin, D Present, Dept. of Medicine, Mount Sinai Medical Center, New York, NY.

Metronidazole (M) provides effective therapy in selected cases of Crohn's disease (CD). Its use has been limited, however, by a high incidence of side effects, particularly the development of peripheral neuropathy (PN). We retrospectively surveyed all patients in our practice with CD who received M ($N = 81$) to identify: a) incidence of PN, b) possible factors predisposing to PN, c) duration of PN, and d) resolution of PN after discontinuing M. The diagnosis of PN was made clinically, manifested as paresthesias of the extremities; EMG's were not performed. We followed all PN+ patients after discontinuation of M to determine duration of PN.

Results: PN developed in 20 (25%) of patients with CD receiving M. PN+ patients did not significantly differ from PN− in terms of age, sex, anatomic distribution of CD, presence of internal or perianal fistulae, or previous intestinal resection. Concomitant or previous medications were as likely in both groups to include steroids, immunosuppressives, or other antibiotics. Exposure to M prior to developing PN was not significantly different from that of PN− patients with respect to: total dose, days of M therapy, average daily dose, exposure to doses above 1G/day, or iv vs po administration.

Table: Once PN developed it lasted for an average of 311 days after discontinuation of M. In 2 patients PN has persisted for more than 3 years.

	PN+	PN−
N	20	61
Avg Ttl M	320G	367G
Avg Ttl M Days	286	319
Avg Daily M Dose	1.12G	1.15G
High Dose M	50%	41%
IV M	15%	11%

Peripheral Neuropathy in Crohn's Disease Patients Treated with Metronidazole: Who Develops It? How Long Does It Last? (*continued*)

Conclusion: PN developed in 25% of CD patients treated with M. No demographic, clinical or pharmacologic factors distinguished PN+ from PN−. Despite cessation of M, average duration of PN was 311 days and has persisted for more than 3 years in 2 of the 20 PN+ group.

Hematology

Antiidiotypic Antibodies to Antiplatelet Antibodies in Intravenous Gammaglobulin. Lisa J Cardo, James R Keenan, James B Bussel, Thomas Kunicki, and Charlotte Cunningham-Rundles.

Immune thrombocytopenic purpura (ITP) is characterized by the presence of antiplatelet antibodies which result in the destruction of platelets by the reticuloendothelial system. Several investigators have found that antibodies against platelet membrane glycoprotein antigens (predominantly the GP IIb/IIIa and Ib/IX complex) can be found in the sera of the majority of patients with ITP. One successful method of treatment of ITP involves the administration of high dose intravenous gamma globulin (IVGG). There is evidence to suggest that Fc receptor blockade occurs, but antiidiotypic interactions may also contribute to the mechanism of action of IVGG.

We have obtained evidence which suggests that IVGG preparations contain antiidiotypic antibodies directed against monoclonal antiplatelet antibodies. We have tested the effect of IVGG on preventing the binding of a panel of four murine monoclonal antiplatelet antibodies, directed against either the GP IIb/IIIa or Ib/IX complex, to human platelet membranes used as target antigens in ELISA. Pharmacologic concentrations of IVGG resulted in a dose dependent blocking of the binding of the mouse antiplatelet antibodies to the platelet membranes. Blocking also occurred with F(ab)2 fragments of IVGG, but no blocking was found when intact myeloma proteins or the gamma globulin of normal controls were tested at the same concentrations. This suggests that the blocking effect is mediated by the antigen combining portion of the antibody molecule.

These data present direct evidence that human antiidiotypic antibodies can be found in pooled human immunoglobulin, and can interfere with the binding of specific antiplatelet antibodies to platelet membrane glycoproteins in ITP. Such antibodies could potentially exert regulatory influence on the production of antiplatelet antibodies in this disease, and contribute to the observed benefits of IVGG.

Production of Antiidiotype to Anti D in Response to the Administration of RH Immune Globulin. Lisa J Cardo, Charlotte Cunningham-Rundles, Pablo Rubinstein, and Richard E Rosenfield.

Rh immune globulin is administered to Rh negative women to prevent alloimmunization to the fetal D antigen during and after pregnancy. Fetal Rh positive cells entering the maternal circulation potentially become coated with Rh immune globulin, and then can be rapidly cleared by the reticuloendothelial system. However, it also appears possible that the administration of Rh immune globulin, could result in a suppressive effect on maternal anti D production, potentially by stimulating the production of antiidiotype antibodies (anti-anti D).

We have demonstrated the presence of antibodies which fulfill the criteria of antiidiotype to anti D, by hemagglutination of anti D coated cells, in 83 samples of serum from 19 women who had received Rh immune globulin, and not in the serum of 65 samples from 15 male and female controls. This agglutination was not seen when red cells were coated with a wide variety of antibodies other than anti D, nor when Fab′ fragments of anti D were utilized. This antibody was also demonstrated by ELISA in 69 patient samples, but not in 60 control samples, and showed specificity for the anti D present in Rh immune globulin. Using Rh immune globulin and two human monoclonal anti D antibodies, antiidiotype antibodies were found in 60 of 69 serum samples tested. By ELISA this antibody activity was demonstrable as both IgM and IgG. In the case of both hemagglutination and ELISA, the antibody activity in maternal sera could be inhibited by pooled Rh positive serum (containing the D antigen), but not by pooled Rh negative serum (lacking the D antigen), and not by the isolated immunoglobulins of either group.

We conclude that Rh immune globulin administration results in the production of antiidiotype to anti D. Further investigation is necessary to determine whether or not this antibody is responsible for the immunoprophylaxis which occurs with administration of Rh immune globulin.

Acquired Dysfibrinogenemia in Patients with the Acquired Immune Deficiency Syndrome. Lisa J Cardo, Joseph S Latino, Aldona Wos, Stanley L Lee, Angelica B Miotti.

Eleven consecutive patients with the acquired immune deficiency syndrome (AIDS) who unexpectedly bled significantly (>50 cc) at transbronchial biopsy were screened for abnormalities of hemostasis. A clinical diagnosis of acquired dysfibrinogenemia was made. All patients were noted to have prolonged thrombin times which persisted upon mixing with control plasma. Reptilase times were also prolonged and fibrin degradation products were absent.

The fibrinogen of two patients was isolated and was noted upon testing to have a prolonged thrombin time, and to prolong the thrombin time of control plasma. Fibrin monomer polymerization was delayed in onset, and the rate of polymerization was decreased when compared with controls. Upon treatment with neuraminidase the thrombin time and the fibrin monomer polymerization corrected.

Acquired dysfibrinogenemia is routinely associated with minimal in vivo hemostatic defects, in spite of marked prolongation of the thrombin time. Minimal bleeding within the bronchial tree, however, can be life threatening. In this regard, the presence of an acquired dysfibrinogenemia could lead to significant bleeding at broncoscopy.

Antiidiotype to Antiplatelet GP IIb/IIIa and Ib/IX in RH Immune Globulin. Lisa J Cardo and Charlotte Cunningham-Rundles.

Rh immune globulin has been utilized experimentally as an alternative to intravenous gamma globulin for the treatment of patients with Immune Thrombocytopenic Purpura (ITP). It has been utilized in much lower doses than IVGG, and has been less successful overall. Better responses occur with higher doses and more frequent treatments. The therapeutic mechanism of Rh immune globulin in ITP may be related to a flooding of the reticuloendothelial system by immune complexes, since Rh positive individuals do undergo some hemolysis after administration. There is evidence that antiidiotypes to antiplatelet antibodies may play a role in the mechanism of IVGG in ITP. A similar effect could be occurring in patients who receive high doses of Rh immune globulin. We have tested the effect of Rh immune globulin in preventing the binding of a panel of 4 murine monoclonal antiplatelet antibodies directed against the GP IIb/IIIa and Ib/IX complexes, to platelet membranes on ELISA.

Concentrations of Rh immune globulin used clinically resulted in a dose dependent blocking of binding of the mouse antiplatelet antibodies to the platelet membranes used as antigen targets on ELISA. Blocking also occurred with F(ab)2 fragments of Rh immune globulin, but was not achieved when intact myeloma proteins or the gamma globulin of normal controls were tested at the same concentrations. This effect therefore appears to be mediated via the antigen combining portion of the antibody molecule. This suggests that the blocking effect involves an idiotype-antiidiotype mechanism as has been seen with IVGG. The therapeutic efficacy of Rh immune globulin in ITP could theoretically be improved by the use of higher doses. This application could be limited in Rh positive individuals, but could result in successful treatment of Rh negative individuals in whom high doses could be employed.

Infectious Diseases

The Significance of Isolated Positive Cerebrospinal Fluid Cryptococcal Antigen in HIV-Infected Patients. Alejandra Gurtman, Joseph Masci, Gerald Pierone, Peter Nicholas, Division of Infectious Diseases, Mount Sinai Services, Elmhurst Hospital, Elmhurst, NY (Box 8000).

Objective: To determine the incidence and significance of isolated positive (+) cryptococcal antigen assay (CA) from CSF in HIV+ patients (pts).

Methods: All CA performed between 12/87 and 4/89 were identified. Cases in which CA was + in the cerebrospinal fluid (CSF) but not in the serum and cultures were negative were regarded as isolated positive (IP) tests. Records of these pts were reviewed for other evidence of cryptococcal infection (CI), HIV status and amphotericin B therapy (AmB).

Results: 48 of 635 CSF specimens (7.5%) tested + for CA. Of the 48 + tests, 27 (56%) had + CSF cultures and were eliminated from the analysis. Inverse CSF titers in this group were 4 to 10240 (mean = 1618). Of the remaining 21 + results, 10 were from 10 HIV− pts and were excluded. 11 (23%) were from 9 HIV+ pts. Inverse titers in the HIV+ pts were 1 to 20 (mean = 4.9). 2 of 9 (22%) HIV+ pts received therapeutic courses of AmB. Of the 7 pts who received no therapy, 1 (14%) was found to have active CI 6 months (m) after the initial + CA (regarded as true +), 3 (42%) had no evidence of active infection on followup of 3 to 11 m (possible false +), 1 (14%) had no evidence of CI at autopsy 1 m after initial + CA (definite false +), incomplete data was available on the remaining 2 pts.

Conclusion: Isolated + CSF CA tests were common in HIV+ pts. Titers were substantially lower than in cases where CI was documented by other means. A significant proportion appear to be false +. Supporting evidence of CI should be sought in such cases prior to the institution of AmB if the clinical condition of the patient is stable.

Molecular Biology

Corticosteroids Inhibit Induction of the JE Gene by PDGF and Serum in Vascular Smooth Muscle Cells. Michael Poon, Hong Zhang, Claire-Lise Rosenfield, Barrett J Rollins, and Mark B Taubman, Molecular Medicine Unit, Department of Medicine & Brookdale Center for Molecular Biology, Box 1128A, Mount Sinai School of Medicine, NY.●

Abnormal growth and migration of vascular smooth muscle cells (VSMC) is a major feature of atherosclerosis. Corticosteroids inhibit proliferation and migration of cultured VSMC. To investigate the molecular mechanisms underlying corticosteroid effects on VSMC, we have examined the expression of JE, a secretory glycoprotein that functions in part as a monocyte and VSMC chemoattractant. Increased levels of JE mRNA and protein have been found in cultured VSMC treated with platelet-derived growth factor (PDGF) and in rat aortas 2–4 hrs after balloon injury.

In the present study, rat aortic VSMC were made quiescent by a 48 hr incubation in medium containing 0.5% calf serum (CS) and then treated with growth factors (20 ng/ml PDGF-BB or 10% CS). JE mRNA was rapidly induced by both growth factors, with maximal levels seen 1–2 hr after treatment. Concomitant treatment of VSMC with 1 μM dexamethasone (Dex) and either PDGF or 10% CS blocked the induction of JE by either growth factor. Significant inhibition occurred with as little as one hour of Dex treatment and was maximal by 4 hr. In addition, pretreatment of quiescent VSMC with Dex (1 μM for 48 hr) also blocked induction of JE, even when these cells were subsequently incubated with fresh medium containing no Dex for an additional 72 hr prior to serum stimulation. Therefore the inhibitory effect of corticosteroids on JE appeared to be both rapid and long-lived. Inhibition of JE was dependent upon relative glucocorticoid activity with maximum inhibition occurring at 1–10 nM Dex, 10–100 nM hydrocortisone, and 0.1–1 μM fludrocortisone. Testosterone and progesterone had no effect on the induction of JE mRNA at up to 100 μM. The protein synthesis inhibitor cycloheximide (10 μM) completely blocked the effect of Dex, demonstrating that protein synthesis was necessary for corticosteroid mediated inhibition of JE expression. This is in contrast to most other corticosteroid responsive genes, for which corticosteroid stimulation or inhibition does not require protein synthesis.

In summary, JE is the first "early" growth-response gene found to be inhibited by corticosteroids. The mechanism of inhibition appears to be different from that of other known corticosteroid inhibitable genes. Further study of JE may provide important insights into the mechanism by which corticosteroids mediate VSMC growth and migration as well as inflammation.

The JE Gene Encodes a Smooth Muscle Chemotactic Factor That Is Induced by Vascular Injury. Jonathan D Marmur, Victor L Friedrich Jr, Maria Rossikhina, Barrett J Rollins, Mark B Taubman, Mount Sinai School of Medicine, New York, NY & Harvard Medical School, Boston, MA.●

Vascular smooth muscle cell (VSMC) migration is fundamental to atherosclerosis and restenosis. In culture, platelet-derived growth factor (PDGF) induces migration of VSMC. It has recently been reported that the PDGF-inducible gene, JE, encodes a monocyte chemotactic factor.

To examine whether JE is also chemotactic for VSMC, migration assays were performed using a modified Boyden chamber. Culture medium from COS-7 cells transfected with mouse JE cDNA served as a source of JE protein; medium from cells transfected with JE cDNA in the antisense orientation served as control. JE-containing medium (1:10 dilution) induced a 2-fold increase in VSMC chemotaxis as measured by nuclei/high power field (188 ± 17 vs 93 ± 17 for control; $p = 0.0025$). Purified human recombinant JE also induced VSMC chemotaxis (128 ± 18 at 10 ng/ml; 76 ± 11 at 1 ng/ml; 43 ± 18 for medium alone). To determine whether JE plays a role in vivo, rabbit aortae were subjected to balloon dilatation (BD), and mRNA was isolated. Using a mouse JE riboprobe, induction of the gene was detected at 1 hour after injury; the level of gene expression remained elevated up to 4 hrs following BD. To detect induction at the protein level, rat aortae were subjected to BD and sections were stained with antibody directed against rat JE. Whereas normal vessels exhibited low levels of immunoreactive JE protein, dilated vessels exhibited high levels with 4 hrs of injury. The time course of gene induction and protein synthesis seen in vivo closely mimic that seen in cultured VSMC treated with PDGF.

Thus, induction and secretion of HE is an early response to vessel injury that may mediate PDGF-induced migration of VSMC. We have demonstrated the in vivo induction of a gene and demonstrated a novel function for its protein that appears to be related to the pathogenesis of atherosclerosis and restenosis following angioplasty.

Nephrology

Cloning the Rat Prepro Epidermal Growth Factor Gene. Subodh Saggi, Peter Price, and Robert Safirstein, Renal Division and Department of Biochemistry, Mount Sinai School of Medicine.●

Renal cell injury, whether induced by cisplatin injection or renal artery clamping, is accompanied by changes in gene transcription. The mRNA levels of several so-called early growth response genes, like c-fos and Egr 1, respond rapidly to injury and hive kinetic characteristics that are typical of their response to mitogenic stimuli. By contrast, the mRNAs of preproEGF and Tamm-Horsfall fall rapidly following renal cell injury. The reduction in these related mRNAs occurred over a prolonged period of time and overlapped the period of increased DNA

Cloning the Rat Prepro Epidermal Growth Factor Gene. (*continued*)

synthesis that characterizes the recovery phase of acute renal failure. Kidney levels of preproEGF and Tamm-Horsfall mRNA appear only after birth in the developing kidney, suggesting similar regulation after renal cell injury.

We have begun to characterize preproEGF cDNA in the rat as a first step to study mRNA regulation in the kidney. RNA was prepared by the guanidinium thiocyanate method and cDNA synthesized from the poly(A) fraction. The cDNA was inserted in an M13-derived expression vector and the DNA used to transfect Escheriichia coli MC1061/p3. The resultant library was screened initially with a mouse preproEGF cDNA and later with a rat probe. Four positive clones have been identified which overlap the reported mouse and human cDNA nearly completely. These clones were sequenced by the dideoxy chain termination method. To date the sequencing of these clones reveals a nearly 70% homology between rat, mouse, and human EGF sequences. In one of the clones, a deletion of an exon occurs at the splice-acceptor site indicating organ or species specific post-transcriptional processing. Using a rat 5′ probe derived from our sequenced cDNA, we have screened a rat liver genomic library in lambda gt 11 and identified three clones that we are sequencing.

We hope to study the factors that determine preproEGF expression to define more clearly the role of preproEGF in renal regeneration and development.

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Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events was due to the drug.

Axid® (nizatidine, Lilly)

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to three times the upper limit of normal, however, did not significantly differ from that in placebo patients. Hepatitis and jaundice have been reported. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Because cross-sensitivity among this class has been observed, H_2-receptor antagonists should not be administered to those with a history of hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

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Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience

David B. Sachar, guest editor

From the Division of Gastroenterology, Mount Sinai Medical Center

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Introduction

DAVID B. SACHAR, MD

IBD Therapies for the 1990s: Scientific Basis and Clinical Experience

THIS SPECIAL symposium is a look ahead, forecasting the future directions for inflammatory bowel disease therapy in the 1990s. It concentrates principally on the scientific basis for the newer therapies of inflammatory bowel disease (IBD), including 5-aminosalicylate preparations, nonsystemically acting steroids, 4-aminoquinolones, antimetabolites, and cyclosporine. Then, on the basis of that science, clinical experiences with some of the newer agents are examined.

An all-star international cast of authors has been assembled for this purpose, representing six medical centers throughout the United States and two medical centers abroad. Even more importantly, our authors represent multiple disciplines. Besides the usual gaggle of gastroenterologists, we have the benefit of experts in autoimmunity, bone metabolism, and nephrology, all of whom have important lessons to convey regarding the pathogenesis and treatment of inflammatory bowel diseases.

Specifically, Richard MacDermott sets the stage with a comprehensive yet lucid overview of immune mechanisms in the pathogenesis of inflammatory bowel diseases. Lloyd Mayer follows up by focusing on new concepts of the immunoregulatory functions of intestinal epithelial cells, their derangements in Crohn's disease and ulcerative colitis, and their modulation by novel therapeutic interventions.

Next, we are brought up to date by Stephen Hanauer on the latest strategies for improving delivery systems of 5-aminosalicylic acid, the active moiety of both old drugs like sulfasalazine and new drugs like mesalamine and olsalazine. Corticosteroids are the subject of the subsequent two articles: I outline the pharmacologic principles of the new generation of nonsystemically acting steroids, and Derek Jewell reviews their recent clinical track record. Burton Korelitz then discusses the whole spectrum of antimetabolite therapy from both controlled and uncontrolled studies of efficacy to meticulously recorded and authoritative observations on side effects and complications.

In a remarkable display of interdisciplinary cross-fertilization, R.G.G. Russell demonstrates the vast therapeutic potential of immunodulation, using metabolic bone disorders as a most enlightening model of disease and cyclosporine as a model of therapy. The next three articles pursue the cyclosporine story further: John Carstens surveys the world's experience with cyclosporine in autoimmune diseases like multiple sclerosis and rheumatoid arthritis; Simon Lichtiger reviews up-to-the-minute results of cyclosporine trials in ulcerative colitis and Crohn's disease; Gerald Appel focuses on the intricate relationships between cyclosporine and the kidney.

Finally, Henry Janowitz tackles the broader issues involved in assessing the therapeutic efficacy of various drugs as he brings to bear the specialized techniques of meta-analysis.

It took extraordinary efforts on many fronts to put a program like this together. For its efforts on behalf of the original symposium on which this issue is based, I want to acknowledge the support of the Page and William Black Postgraduate School of Medicine of the Mount Sinai School of Medicine of the City University of New York. The logistics of the conference, held December 8, 1989, in New York City, were masterfully arranged by the extraordinary efforts of The Crohn's and Colitis Foundation of America (formerly the National Foundation for Ileitis and Colitis), particularly the Greater New York Chapter: Joan Telley and a devoted staff.

Sandoz Pharmaceuticals Corporation not only underwrote the costs of the conference and partially supported the costs of publishing this issue of *The Mount Sinai Journal of Medicine*, but also provided much of the intellectual and organizational thrust for the program, and in addition sent their director of medical research, John Carstens, to join the faculty. We appreciate the efforts of Bob Clark and Larry Kupferschmidt and others at Sandoz.

Finally, I want to acknowledge my Mount Sinai colleagues, Simon Lichtiger and Daniel Present, who really conceived and initiated the whole concept of producing a symposium of this type.

This symposium considers the scientific basis from which clinical experience derives. To set the stage for this scientific basis, an outstanding gastrointestinal immunobiologist at the forefront of inflammatory bowel disease research discusses the immune system in inflammatory bowel disease. In addition to his work as an immunobiologist, Richard MacDermott has also been a leader of activities at the national level in his many capacities on the public front, his long chairmanship of the Grants Review Committee of The Crohn's and Colitis Foundation of America, and his current T. Grier Miller Professorship at the University of Pennsylvania, in addition to his directorship of the Gastroenterology Section of the Department of Medicine at that university.—DBS

The Immune System in Inflammatory Bowel Disease

RICHARD P. MACDERMOTT, M.D.

THE IMMUNE system is involved in the pathophysiology of inflammatory bowel disease (IBD) through a sequence of immunologic steps, beginning with initial antigen processing events (1–3). The precise nature of the antigens that initiate IBD are unknown at this time.

Initiating Events

Nevertheless, of the potential etiologic factors that have been suggested, a major focus is now being placed on bacterial cell wall products, including peptidoglycans, FMLP, and LPS. These molecules nonspecifically induce an intense activation of macrophages, granulocytes, and lymphocytes, all of which are present in great abundance in IBD lesions. Thus, bacteria—through the effects of their cell wall products or toxins—could be involved either as primary or secondary events in initiating or perpetuating IBD (1–3). This had led to the working hypothesis on IBD that, in a genetically predisposed individual, ubiquitous and common bacterial cell wall products and molecules capable of initiating and activating an inflammatory immune response initiate a sequence of immunologic processes that are not appropriately downregulated (1–3). Initiating events then lead to macrophage activation, with the resultant production of large amounts of interleukin 1 and 6 and tumor necrosis factor. Subsequent cell-mediated immunologic events involve the mucosal immune system, and lead to the chronic intestinal destruction associated with IBD (1–3).

Epithelial M Cells and the Homing Process. Although we may not always regard cell-mediated immunity as a primary intestinal function, in actuality the mucosal immune system is the largest immunologic tissue in the body (4). Furthermore, because so many intestinal bacteria and viruses are potentially pathogenic, the mucosal immune system is vital for normal health.

Specialized epithelial cells, termed M cells, cover Peyer's patches and lymphoid follicles and allow the specific transport of viruses and large antigens into contact with underlying lymphocytes and macrophages (5, 6). After antigens are processed and presented to immature lymphocytes in the Peyer's patch areas, lymphoblasts mature outside the intestine during a "maturational journey" through the lymphatic system and circulation, after which they "home" back to the intestine as mature cells, which reside in the lamina propria (7).

In addition to lamina propria mononuclear cells, the intestine also has a unique subcompartment of cells, intraepithelial lymphocytes (8, 9),

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Adapted from the author's presentation at the seminar "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" held at the Mount Sinai Medical Center on December 8, 1989. From the University of Pennsylvania School of Medicine. Address reprint requests to the author, who is T. Grier Miller Professor of Medicine and Chief, Gastrointestinal Section, University of Pennsylvania School of Medicine, at Clinical Research Building, Suite 600, 422 Curie Boulevard, Philadelphia, PA 19104-6144.

which are predominantly T cells residing between intestinal epithelial cells. Intraepithelial lymphocytes are of the cytotoxic/suppressor cell phenotype (predominantly CD8-positive) and also bear a unique subcomponent of the T-cell receptor, the majority in animals being gamma/delta-bearing T cells (10, 11). Interestingly, intraepithelial lymphocytes (8, 9) and gamma/delta T cells (10, 11) are markedly increased in the small intestine in patients with gluten-sensitive enteropathy (12, 13).

A number of infectious agents, such as reovirus (6), adhere specifically to M cells (5) but do not adhere to surrounding epithelial cells and can then be transported across the M cells into the underlying lymphoid follicle or Peyer's patch in order to allow antigen processing and presentation by macrophages and lymphocytes. Thus, although we usually think of the intestine as providing a rigid barrier to luminal antigens, M cells provide a way to sample the unique microbial environment located in the intestinal lumen. This is a critical component of providing effective host defense mechanisms. However, M cells also can provide a portal of entry for viruses and bacteria that can adversely affect the host.

Peyer's patch lymphocytes are immature after antigen sensitization, and one might expect that the simplest process would be for the cells to directly migrate into the nearby lamina propria and mature. Instead, primed cells leave the intestine and migrate via the lymph nodes, efferent lymphatics, and thoracic duct, during which time they begin to mature into lymphoblasts (7, 14). They then circulate in the peripheral blood and subsequently home back to the gastrointestinal mucosa as well as other secretory sites (7, 14).

The unique intestinal antigen recognition system, therefore, allows large molecules in the gut to be transported by M cells, presented by epithelial cells or underlying macrophages to Peyer's patch or follicle-associated lymphocytes, which then mature outside the gastrointestinal tract. While the cells undergo their maturational journey, they become immunocompetent and home back to a number of other mucosal surfaces in addition to the gut.

One of the best clinical examples of the homing process has been the demonstration that nursing mothers fed nonpathogenic bacteria will secrete specific antibodies in their breast milk that are protective against the orally administered bacteria (15). This may provide a way for passive immunity against enteric organisms to be transferred from mother to nursing infant (7, 14, 15).

The mechanisms of lymphoblast homing (16, 17) involve high endothelial venules, which are large cuboidal cells, that have specific antigens on their surface, termed addressins (18), which interact with organ-specific "homing" receptors on mature lymphoblasts. The cell surface interactions between lymphoblasts and high endothelial venules thus determine the sites to which lymphoblasts will migrate; specific receptors on Peyer's patch or intestinal lymphoid follicle cells direct cells to home back to intestinal mucosal sites, as opposed to peripheral node sites (16–18). Because these studies were carried out in animal models, we have sought to study the homing receptors present on normal intestinal lamina propria mononuclear cells in collaborative studies with Sirpa Jalkanen.

Homing Receptors on Normal Human Cells. We found that unseparated normal human lamina propria mononuclear cells bind poorly to peripheral lymph node high endothelial venules and thus do not have marked numbers of homing receptors for peripheral lymph nodes, whereas they do bind well to intestinal mucosal high endothelial venules (19). A subgroup of large lymphoblast cells from normal human intestine, which are predominantly IgA-bearing (about 60% IgA-positive) and which also contain T cells that have IgA Fc receptors on them, bind avidly to mucosal high endothelial venules (19).

Thus, in humans as well as in animals, there do appear to be cells in the lamina propria with homing receptors on their surface which direct the cells to the intestinal sites. Moreover, using monoclonal antibodies, as well as polyclonal antibodies, the binding of normal human lamina propria mononuclear cells to mucosal high endothelial venules could be blocked, indicating that these are indeed cell-surface homing-receptor-related events (19). As we learn more about the mucosal immune system in relation to inflammatory bowel disease, we may better understand the lymphoblast homing mechanisms involved in directing lymphoblasts to migrate specifically to sites of inflammation in ulcerative colitis and in Crohn's disease.

A number of areas appear particularly fruitful for future research on initiating factors in IBD. First, the study of bacterial cell wall products (peptidoglycans, FMLP and LPS) and bacterial toxins, as initial stimulating factors in the intestinal immune response and intestinal inflammatory reaction, will provide a way to examine bacterial products commonly present in the intestinal tract that incite important immunologic and inflammatory events. A second area of tremendous promise is epithelial-cell presentation of antigens and M-cell transport of molecules allowing antigens to be directly processed by the cells of the mucosal immune system. Third, we need to know a great deal more about our host defense mechanisms and the mucosal immune system, with applied emphasis on mechanisms of cell trafficking, lymphocyte activation, and lymphoblast homing in disease states such as inflammatory bowel disease and gluten-sensitive enteropathy. Fourth, the characterization of intraepithelial lymphocytes and the regulation of epithelial cell growth and regeneration will help us understand the initiating and reparative events in IBD.

Mechanisms of Injury

Once intestinal inflammatory processes are initiated, subsequent events include both nonspecific, “innocent bystander” target cell destruction and direct cell-mediated and antibody-mediated autoimmune injury to the intestine (1–3). Thus, the effector mechanisms of injury in IBD involve both cell-mediated memory and nonspecific proinflammatory events (1–3). The cell-mediated memory and effector events in IBD involve a sequence of carefully regulated steps. After production of large amounts of interleukin-1 by macrophages and other cell types, T-cell activation occurs, resulting in the clonal expansion of a variety of T-cell subclasses. Production of cytokines leads to expansion of helper T cells, and the resultant enhanced antibody synthesis and secretion results in the heightened activation of immune function. Normally, cytotoxic function by intestinal mononuclear cells is quite reduced and quiescent until activated by interferon, lectins, or cytokines (20–22). Cytotoxic capabilities of intestinal mononuclear cells are not increased in IBD (20–22). At this point, there is no good evidence that cytotoxicity by lymphocytes plays a major role in immune-mediated injury to the intestine in IBD (1–3).

Normally, IgA is the dominant and most important immunoglobulin in the gut, since it provides the initial protective mucosal defense mechanism (23, 24). However, secretion of IgA by intestinal B cells in inflammatory bowel disease is actually decreased (25, 26) and not as prominent as one might think if IgA were the major immunoglobulin involved in IBD.

In contrast, we have found an enormous increase in production of IgG by IBD intestinal lamina propria mononuclear cells (27–29). Interestingly, there is a marked difference between the IgG subclasses secreted by ulcerative colitis and Crohn’s disease intestinal lamina propria mononuclear cells. IgG1 and IgG3 subclasses are dominantly expressed in ulcerative colitis, whereas IgG2 subclass is predominant in Crohn’s disease (28, 29). Using monoclonal antibodies and immunohistochemical studies, other workers have found similar results; that is, IgG1 is markedly increased in ulcerative colitis, and IgG2 is increased in Crohn’s colitis (30). In carrying out an analysis of IgG subclasses using serum in a multicenter collaborative study, we found similar alterations in the sera of patients with IBD (31). Compared to normals, total serum IgG levels are increased in both ulcerative colitis and Crohn’s disease, IgG1 again being dominant in active ulcerative colitis sera, and IgG2 in active Crohn’s disease sera (31). These changes in the serum most likely reflect immunologic alterations in intestinal tissue in active IBD (31).

These observations are of interest because IgG subclasses have very different functional capabilities. IgG1 represents the dominant response to proteins and T-cell-dependent antibody responses (28, 29). IgG2 and IgG4 subclass deficiencies can be found in children who have meningitis, pneumonia, and other recurrent infectious processes. IgG1 and IgG3 are much better complement pathway activators and are better at promoting opsonization than IgG2 (28, 29). IgG1 and IgG3 may therefore be particularly capable of inducing intestinal tract injury. Although in the normal intestine IgA is the major immunoglobulin of importance, in inflammatory bowel disease, IgG, with its ability to fix complement, may be pivotal in inducing intestinal injury and inflammation (1–3, 27, 28).

With regard to direct autoimmune injury and cell-mediated events in IBD, there are a number of exciting areas of research in which progress during the next 8 to 10 years is needed and toward which further investigations should clearly be directed. First, the activation of lymphocytes and macrophages, the subsequent production of cytokines, and the resultant immunoregulatory alterations are important. Second, the availability of specific cytokine inhibitors and receptor antagonists will allow the role of lymphokine pathways in IBD to be explored at the clinical level. Third, the induction of cell-mediated cytotoxicity remains of interest particularly in regard to ways of increasing host defense mechanisms for the intestine. Fourth, the role of IgG and IgG subclasses in inducing intestinal injury, and the nature of the antigens against which the IgG antibodies are directed, will be critical. Regulation of granuloma formation, particularly investigating the production by granulomas of a variety of neuropeptides and cytokines secreted from the inflammatory cells that constitute the granuloma, provides a fifth important investigational area. Finally, the cell-mediated and cytokine-regulated mechanisms that influence collagen production by smooth muscle cells need to be understood to elucidate the mechanisms of stricture formation in Crohn's disease.

These latter three subjects (IgG subclasses, granuloma formation, and stricture formation) are also important to focus on because they are areas which demonstrate clear immunologic differences between Crohn's disease and ulcerative colitis. Ulcerative colitis and Crohn's disease are different disease processes clinically. We therefore need to understand much better why there are granulomas in Crohn's disease and not ulcerative colitis, why differences between IgG subclasses occur in these two disorders, and what immunologic processes lead to fibrosis and stricture formation, primarily in Crohn's disease.

Inflammatory Mediators. One of the results of a highly activated mucosal immune system is the triggering of nonspecific inflammatory processes. It is in this area that most of our current drug therapy is aimed, in that steroids, 5-ASA, and immunosuppressives all inhibit the nonspecific inflammatory processes seen in IBD (1–3). Because of the constant and rapid influx of granulocytes and macrophages in both ulcerative colitis and Crohn's disease, there are large numbers of inflammatory mediators released, including prostaglandins, leukotrienes, platelet activating factor, and oxygen radicals, which then produce severe, nonspecific injury to epithelial cells and other cells of the gastrointestinal tract (1–3).

The first inflammatory mediator examined was prostaglandin E2, which was found to be produced in markedly increased amounts in inflammatory bowel disease (32). However, the use of nonsteroidal drugs and cyclo-oxygenase inhibitors actually exacerbated IBD in certain patients (33, 34). The explanation for this was not entirely clear until the inhibition of the 5-lipoxygenase pathway by 5-ASA and the markedly increased production of leukotriene B4 in inflammatory bowel disease were described (35, 36).

Leukotriene B4 is a potent chemoattractant and plays an important pro-inflammatory role in IBD. Interestingly, in studies of inflammation in animal models, prostaglandins have been shown to actually protect the mucosa. Thus, it may be important to learn which parts of the arachidonic acid metabolism pathway are blocked by pharmacologic agents. Drugs preferentially blocking the 5-lipoxygenase pathway appear to lead to the production of more protective and less destructive inflammatory mediators. Steroids work by many different mechanisms, one of which may be the decreased production of endogenous arachidonic acid from membrane phospholipids, leading to a decrease in both prostaglandins and leukotrienes. We need to know much more about the cells of origin of inflammatory mediators in the intestine. Furthermore, studies are just beginning with regard to the effects of LTC4, CTD4, and LTE4 on vascular permeability and smooth muscle contraction.

5-Aminosalicylic acid is an oxygen radical scavenger and will also lead to a decrease in the production of oxygen radicals. Oxygen radicals are made in large numbers by the tremendous influx of macrophages and granulocytes into inflammatory intestinal lesions (37, 38). Normally oxygen radicals are degraded by a series of enzymes (superoxide dismutase, catalase, glutathione peroxidase) so that they do not damage the tissue. In a series of studies carried out in collaboration with Matt Grisham, we examined the levels of these enzymes in the intestinal mucosa. Interestingly, the levels of protective enzymes—both superoxide dismutase and glutathione peroxidase—are low in normal intestinal mucosa (39). Thus, the gastrointestinal tract is an environment in which large numbers of oxygen radicals are likely to easily overpower normal protective mechanisms.

In summarizing the sequence of events that lead to the inflammatory processes, which occur in IBD (1–3), the cytokine and cell-mediated regulation of immunoglobulin production may be important because of the ability to trigger complement-pathway as well as macrophage activation. A number of processes may account for the large influx of macrophages and granulocytes, including cytokines (such as IL-8 and others), complement activation, and LTB4. Once the influx of macrophages and granulocytes occurs, a markedly increased production of oxygen radicals, proteases, LTB4, platelet activating factor, and other mediators leads to what we see clinically as the final inflammatory processes in the intestine (1–3).

Future Research Directions. In the future, we need to better understand the transition from chronic cell-mediated events to acute inflammatory events and the downregulation of those processes. Second, the mechanisms of attraction of macrophages and granulocytes to inflammatory lesions in the intestine must be pursued. Third, the examination of leukotrienes and prostaglandins, particularly related to lipoxygenase pathway inhibitors and leukotriene receptor antagonists, will provide effective ways for interrupting these pathways. Fourth, a better understanding of oxygen radicals with regard to both inhibition of production and the development of improved oxygen radical scavengers will be important. Fifth, platelet activating factor and its antagonists will also be exciting to examine. Sixth, a number of human models clearly deserve increased attention. These include the development of pouchitis (in ileoanal anastomosis) and the recurrence of Crohn's disease after resection (to look at disease modifiers and the effect of prophylactic treatment). Seventh, a prospective evaluation of immunologic alterations and genetic markers in family members of IBD patients will provide a system for examining the factors that influence how a patient might tend to develop IBD. Eighth, the culture of normal intestinal epithelial cells, examination of growth factors and better animal models are all important to allow future progress in IBD research to occur. Finally, a better understanding of stress factors, neuropeptides, and neuroimmunologic regulation of the gastrointestinal tract are needed to explore the role of stress and environment in triggering IBD.

During the past decade, excellent progress has been made in elucidating the immunologic alterations which occur in inflammatory bowel disease. Furthermore, understanding the immunopharmacologic mechanisms of drug action has promoted the development of new therapeutic approaches to IBD. As our knowledge of basic immunology and mechanisms of inflammation continues to expand, the cause and immunopathophysiology of Crohn's disease and ulcerative colitis will become more clear.

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We note from Dr. MacDermott's presentation that modern immunologic research is increasingly focussed on events at the tissue level. To intensify this focus, to concentrate on the role of the intestinal epithelial cell itself, and to explore the clinical applications of this research, we call upon someone who is both a gifted basic cellular immunologist and a skillful clinical gastroenterologist, Dr. Lloyd Mayer, director of the Mount Sinai Division of Clinical Immunology.

The Role of the Epithelial Cell in Immunoregulation:

Pathogenetic and Therapeutic Implications

LLOYD MAYER, M.D.

EVERY immune response, normal or abnormal, has to be initiated by one event alone, presentation of antigen. The gastrointestinal tract offers the luxury of several mechanisms by which antigen can cross the physical barrier of mucus, epithelial cells, and M cells and be released into the underlying lamina propria, where lymphocytes, monocytes, and macrophages all participate in an immune response. The interesting phenomenon in the gastrointestinal tract is that we do not mount immune responses to everything that we eat. Dietary and other foreign proteins continuously traverse the gastrointestinal tract, yet no massive immune responses are generated against them. This lack of response seems to run counter to what a normal immune system is supposed to do. I focus on some of the potential pathways that could explain this paradox.

Potential Pathways for Presentation of Antigens. There are three possible mechanisms by which antigen can get through the gastrointestinal tract into the underlying lamina propria: The M cell, the specialized epithelial cell that serves as transport mechanism, sits in the crypts of the villous architecture. Antigen will pass through the M cell, be picked up by underlying macrophages, and travel down to the local Peyer's patches, where a positive immune response will be generated. Several groups have actually demonstrated foreign antigens (such as virus and bacteria) traveling intact through the M cell to the underlying macrophages, which take antigens up and process them.

The M cell is a thin, elongated epithelial cell abutted by adjacent absorptive epithelial cells. However, if one looks at the number and location of M cells, they appear to be a relatively inefficient means of transporting antigen. Depending on the site within the gut, the ratio of M cells to absorptive epithelial cells is anywhere between 1:1000 and 1:100,000. Thus there is a relative paucity of M cells in the gastrointestinal tract.

The Enterocyte. Our laboratory has chosen to focus on a different cell, a cell well recognized as having absorptive capabilities that also has the ability to take up foreign proteins or peptides that have been processed in the gut. This is the conventional enterocyte, or absorptive cell. One can postulate that antigens (for example, bacteria, viruses, digested peptides) come through gut, are taken up and processed in endosomes, and then are cycled back to the surface by a transcellular route. Antigens may also be released into the lamina propria or into the intraepithelial spaces, where other immune cells can potentially become activated.

Model: Immunogenetic Defect in Downregulation. Drawing from such a model for antigen sampling in the gut, we developed a hypothetical model suggesting that inflammatory bowel disease is actually related to the manner in which foreign proteins (bacteria, viruses, and toxins) are handled by the mucosal immune system. This model proposes that no one single agent (toxin, virus, or bacterium) is pathogenic in this process, but that an inherent immunogenetic defect in the

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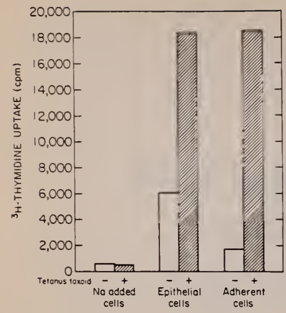

Fig. 1. The most critical experiment in determination of whether epithelial cells could perform functions required of antigen-presenting cells.

ability to handle antigen in the gut causes patients with inflammatory bowel disease (IBD) to generate an active immune response that becomes chronic as a result of failure in downregulating the normal immune response.

Can Gut Epithelial Cells Function as Antigen Presenters? In order to demonstrate the capacity of epithelial cells to function as antigen-sampling or antigen-presenting cells, specific defining criteria for antigen-presenting cells must be met. The initiation of any immune response requires (a) the uptake of antigen by an antigen-presenting cell, such as a macrophage; (b) the processing or breakdown of these large bulky antigens; and then (c) the reexpression of these antigenic peptides in conjunction with self-antigens (MHC [HLA-DR]). This Ag-MHC complex can then activate T lymphocytes (especially helper T cells), which orchestrate the immune response.

We sought to determine whether epithelial cells could perform the functions required of antigen-presenting cells (Fig. 1). In order to stimulate T lymphocytes with tetanus toxoid, antigen-presenting cells (conventionally the adherent cells: monocytes, macrophages, and dendritic cells) must be present. T lymphocytes will not proliferate until the tetanus toxoid has been taken up, broken down, and put back out on the surface of the antigen-presenting cell so that the T-cell receptor can recognize it. Intestinal epithelial cells appear to perform these functions precisely. Highly purified preparations of epithelial cells can take up tetanus toxoid and stimulate the T-lymphocyte proliferative response exactly as do any other antigen-presenting cells.

In contrast to what occurs with conventional antigen-processing cells, in which the predominant response is by lymphocytes of the helper/inducer phenotype (the CD-4 or T4-positive cell), antigen processing through normal intestinal epithelial cells appears to result in the proliferation of suppressor/cytotoxic (CD8-positive) cytotoxic T lymphocytes. Assessment of the function of these cells shows that they act as very potent suppressor T cells, downregulating a variety of immune responses.

These findings make sense intuitively, because a system that is continuously assaulted by foreign bacteria and viruses has to have a mechanism for downregulating or dampening immune responses to all of those exogenous antigens. The selective stimulation of suppressor cells may be just such a mechanism.

The situation seems to be different, however, with gut epithelial cells from patients with IBD. These cells appear to selectively stimulate CD4-positive cells, much like macrophages or other conventional antigen-presenting cells. In other words, there appears to be an inherent defect in the epithelial cells of patients with inflammatory bowel disease that prevents these cells from stimulating CD8-positive or suppressor cells in the way that normal epithelial cells are supposed to. Thus a potential pathogenetic mechanism in inflammatory bowel disease may be that immune responses cannot be normally downregulated or dampened, so that there are inappropriately sustained, enhanced immune responses in the gastrointestinal tract. The T cells that emerge from these interactions are potent helper/inducer T cells (Fig. 2); thus a significant T-cell proliferative response is induced by T cells previously activated by Crohn's disease epithelial cells.

Consequences. The consequences of this phenomenon are actually quite intriguing. We could explain a number of the defects that many groups (as reviewed by MacDermott) have described in inflammatory bowel disease. The key player in this reaction is the CD4-positive T cell, which is being activated inappropriately in inflammatory bowel disease, either by antigen processed in the epithelial cell or by macrophages in the lamina propria.

In any event, these T cells are hyperactivated and consequently secrete a variety of cyto-

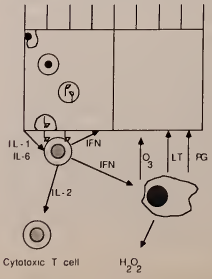

Fig. 2. The consequences of abnormal T-cell activation in Crohn's disease.

kines that can have major effects on other cells in the lamina propria as well as on the overlying epithelial cells. These cytokines include interleukin-2, which can stimulate the generation of cytotoxic T cells; B-cell growth and differentiation factors, which will stimulate the heightened immunoglobulin secretion MacDermott has described; and, perhaps more importantly, γ-interferon (or immune interferon), which stimulates macrophages and thereby causes the secretion of oxygen-free radicals, hydrogen peroxides, leukotrienes, and prostaglandins. These mediators can in time damage overlying epithelial cells and produce edema, granulocyte chemotaxis, and the nonspecific tissue injury occurring in inflammatory bowel disease. If this response cannot be regulated, a chronic, unrelenting inflammatory process will ensue.

Speed of Antigen Processing in Epithelial Cells. What might account for these differences between epithelial cells from patients with inflammatory bowel disease and those from nonaffected people? One explanation might be found in the speed with which antigens are actually handled by epithelial cells. Macrophages process antigen rapidly and efficiently, whereas normal epithelial cells process antigen more slowly. In Crohn's disease, epithelial cell processing of antigen might be too rapid, like that of macrophages, resulting in the inappropriate CD4-positive T-cell proliferation.

To reverse this abnormality in IBD patients' epithelium, one could theoretically use agents that inhibit the rate of antigen processing. For example, lysosomotropic agents such as hydroxychloroquine, chloroquine, or ammonium chloride, which are known to stop the antigen degradative process in monocytes, can do the same thing in the intestinal epithelial cell as well.

Hydroxychloroquine as Inhibitor of Antigen Presentation. When our initial test in vitro of hydroxychloroquine was successful in reversing CD4 and T-cell activation, we began an in vivo clinical trial in patients with ulcerative colitis and Crohn's disease. The response in ulcerative colitis patients with proctosigmoiditis, left-sided colitis, and pancolitis was actually quite dramatic in about 85% to 90% of the cases, reflected not only in clinical and sigmoidoscopic scores but also in our ability to reduce steroid doses. The patients that did not respond were those with fulminant colitis. Patients clinically responded to hydroxychloroquine (Plaquenil) over the course of about 3 weeks to 3 months. The response by patients with Crohn's disease was limited, although, interestingly, patients with colonic disease appeared to respond better (Table).

TABLE
Results of Chloroquine Trial

	Improvement		
	Clinical	Sigmoidoscopy	Reduction in meds
Ulcerative colitis (total)	10/12	10/12	10/12
Proctosigmoiditis	5/5*	5/5	4/5
Left-sided	3/3*	3/3	3/3
Pancolitis	2/4*	2/4	1/4
Crohn's disease (total)	2/6	2/6	1/6
Ileitis only	1/3	NA†	0/3
Ileocolitis	0/2	1/2	0/2
Segmental colitis	1/1	1/1	1/1

* 4/5 and 3/3 in complete remission (proctosigmoiditis and left-sided colitis respectively). No remission in pancolitis. Follow-up 3 months to 1 year.

† Not applicable.

In summary, we now have an agent that is a potent inhibitor of antigen processing and presentation, which appears to be having some therapeutic effect in patients with inflammatory bowel disease.

The potential physiological justification for various therapeutic approaches we currently use is that Plaquenil blocks the initiating event (antigen processing and stimulation of the helper T cell); cyclosporine inhibits secretion of a variety of cytokines; and other agents (such as steroids, sulfasalazine, and even fish oil) inhibit the major mediators of the inflammatory process.

Questions and Answers

Question: Have you done your studies on family members of patients?

Mayer: The problem is that a fair number of epithelial cells is required to do these studies. Until we have a mechanism by which we can study these epithelial cells from biopsies, we won't really be able to perform the appropriate studies.

Barry Worschel, Boston: Lloyd, what percent of normal epithelial cells express class II antigen, and is there any insight into why there might be differences in the immunoglobulin production as a result of this type of antigen presentation, specifically in terms of Crohn's disease and ulcerative colitis with IgG_1 and IgG_2?

Mayer: A good question. Of all the immunologic abnormalities described to date, IgG subclass differences appear to be the most reproducible. Normal small bowel expresses class II antigens. Any inflamed bowel expresses class II antigens, because γ-interferon is a potent inducer of class II antigen (or HLA-DR expression). We are able to demonstrate, using sensitive biotin avidin peroxidase techniques—and Dobbins has likewise demonstrated by EM—that colonic epithelial cells do express DR antigens, whereas M cells don't. But in any inflammatory process, whether it is ischemic colitis or diverticulitis, there is heightened expression of class II antigens. But, interestingly, even in diverticulitis, CD8 suppressor T-cell proliferation rather than a helper response occurs, arguing against nonspecific inflammation as a mechanism to explain our data. T cells secrete a variety of cytokines, some of which are isotype-restricted for IgG_1 and IgG_2. It may be that different populations are sitting within the intestine in patients who have inflammatory bowel disease. The ability to study such a process at this point is, unfortunately, still quite primitive.

To help lead us further along the pathway from scientific basis to clinical experience, the author of this next paper represents the quintessential clinical investigator and interpreter of clinical studies. As a member of the Advisory Panel on Gastrointestinal Drugs to the U.S. Food and Drug Administration, as chairman of the Clinical Affairs Committee of The Crohn's and Colitis Foundation of America, and as an internationally recognized authority on clinical trials and medical treatment of inflammatory bowel disease, Dr. Stephen Hanauer is uniquely qualified to introduce us to the topic of Aminosalicylates: Old and New.—DBS

Aminosalicylates:

Old and New

Stephen B. Hanauer, M.D.

UNTIL the etiology of inflammatory bowel disease is identified and its cure ultimately established, the goal for future therapies will be to modify current treatments to improve their efficacy while reducing their adverse effects. In other words, "diseases that harm call for therapies which harm less." The first practical model for these advances is sulfasalazine and the 5-ASA compounds.

Sulfasalazine

Sulfasalazine is composed of sulfapyridine attached by an azo-bond to 5-aminosalicylic acid. 5-Aminosalicylic acid (5-ASA) has been named mesalamine in the United States and mesalazine in Europe. Over the past twenty years, sulfasalazine has been shown in clinical trials to be effective for mild to moderate acute ulcerative colitis and the maintenance of remission. A dose response has been identified for both acute disease and maintenance of remission in ulcerative colitis. The National Cooperative Crohn's Disease Study and the European Cooperative studies have identified sulfasalazine to be effective in mild to moderate, active Crohn's disease when the colon is involved. To date, it has been difficult to prove sulfasalazine to be effective in maintenance of remission of Crohn's disease, although many clinicians continue to use it as maintenance therapy in Crohn's disease for patients who have responded to it in the active phase. These individuals frequently worsen when sulfasalazine is withdrawn. Hence, there probably is a role for sulfasalazine in maintenance therapy, but that has been difficult to prove in clinical trials.

The major problem with sulfasalazine has been side effects. Many patients are unable to tolerate doses of the drug sufficient for optimal therapeutic effect. Another problem has been inability to deliver the active component (or what we believe to be the active component), 5-ASA, into the small intestine for the patients with Crohn's disease. This probably explains why the drug has not proved very effective for small-intestine Crohn's disease in clinical trials including a number of patients with varying disease locations, severity, and symptoms.

Up to 30% of patients cannot tolerate sulfasalazine because of its common side effects. A much smaller percentage of patients develop either hemolytic anemias, allergic reactions, toxic reactions, or—rarely—worsening of colitis. Moreover, 80% of males develop abnormalities in sperm number or morphology. The exact proportion of these cases that actually result in infertility has not been documented, but in any event the sperm abnormalities are reversible on discontinuation of sulfasalazine with or without replacement by 5-ASA therapy.

The metabolism of sulfasalazine allows the release of 5-ASA into the colon because of azoreductase activity by the intestinal microflora. Most sulfapyridine is absorbed from the colon

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Adapted from the author's presentation at the seminar "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" held at the Mount Sinai Medical Center on December 8, 1989. From the Gastrointestinal Clinical Research Center, University of Chicago Medical Center, Chicago, Illinois. Address reprint requests to the author, who is Director of Gastrointestinal Clinical Research Center, University of Chicago Medical Center, 5841 South Maryland Avenue, Chicago, IL 60637.

and accounts for the great majority of the side effects. Most of the 5-ASA, by contrast, remains in the lumen of the colon. Studies performed at Oxford by Azad Khan and Truelove in the late 1970s used equimolar concentrations of 5-ASA, sulfasalazine, or sulfapyridine in enemas for patients with distal ulcerative colitis. The response to therapy was equal for sulfasalazine and 5-ASA, both being superior to treatment with sulfapyridine enemas, indicating that the 5-ASA was probably the therapeutically active component. Interestingly, these investigators used 2 gm of sulfasalazine or 700 mg of 5-ASA, relatively low doses compared to therapies that we are using today.

Mechanisms of Action. As can be seen from the previous discussions, the exact mode of action of 5-ASA (or sulfasalazine) remains undefined. 5-ASA is a more distal inhibitor of the lipoxygenase pathway and, as MacDermott notes in his article in this issue, they shift more of the arachidonic acid metabolites into the prostaglandins. This reduces the amount of leukotriene B_4 in the lumen (and presumably tissue). In addition, 5-ASA is an inhibitor of reactive oxygen species by inhibiting production and scavenging free oxygen radicals. 5-ASA also inhibits antibody production from plasma cells and is an inhibitor of platelet activating factor and interleukin-1 production. As one can see, there are a number of effects of this compound and we are awaiting specific inhibitors of the lipoxygenase pathway to determine the influence of this metabolic effect.

In any event, it is clear that 5-ASA is interfering with the amplification process of inflammation rather than inhibiting an initiation of inflammation. This may explain why sulfasalazine and 5-ASA are more effective as maintenance therapies than for initial treatment of active disease. It also explains why maintenance therapy is necessary, because the initiating event is still ongoing despite the interference with recruitment of inflammatory cells.

Topical 5-ASA

Subsequent to the clinical studies by Azad Khan and Truelove, Campieri and colleagues in Bologna began to study higher doses of 5-ASA in enema forms for patients with ulcerative colitis confined to the distal colon. They compared standard hydrocortisone enemas (100 mg) to 4 gm 5-ASA enemas. The latter were more effective over a two-week period, with almost twice the clinical effect of the steroid enemas. These studies were followed by a North American placebo-controlled trial over a six-week period comparing the same 4-gm dose of topical 5-ASA with placebo. Sixty-three percent of the patients treated with 5-ASA were "much improved" compared to 29% of the placebo patients. Of note, however, is that 29% of placebo-treated patients did improve, emphasizing the need for placebo-controlled trials in inflammatory bowel disease.

Another problem with clinical trials in IBD is the *definition of response*. The study described above used "much improved" as an endpoint. However, a 50% reduction in symptoms may mean that the patient goes from having ten bloody bowel movements a day to five bloody bowel movements a day. This is not a good clinical response, even though there may be a statistical difference. Furthermore, the six-week duration of the trial did not allow all of the potential responders to be recruited. For instance, when "time to cessation of bleeding" was reviewed by the end of the six-week study, patients were continuing to respond. So we do not know exactly how many patients would have eventually responded or gone into remission; we find that six weeks may be too short a time to evaluate these difficult patients.

We performed studies at the University of Chicago using the same 4-gm 5-ASA enemas in patients who were referred to us for resistant left-sided colitis despite treatment with sulfasalazine, topical or systemic corticosteroids. We found that time to complete remission averaged over 13 weeks. In these refractory patients, a longer trial period is probably necessary when an endpoint such as "remission" is utilized.

Another issue is *dose*. In a double-blind, randomized, controlled trial comparing placebo to 1, 2, and 4 gm 5-ASA enemas using a Pentasa preparation, there was no dose response between 1 and 4 gm over an eight week period. In the United States, the only dose currently available is the 4 gm Rowasa enema (Reid-Rowell), but this dose is probably not necessary in acute disease or for maintenance.

We have also shown that maintenance therapy is necessary for enema treatment. As enema therapy is reduced from nightly to every other night, every third night, and so on, patients experience a gradual flareup of disease. This is a lesson similar to the one learned in experience with sulfasalazine and other 5-ASA agents: maintenance therapy is required. Biddle and colleagues have demonstrated that, over twelve months, nightly 1-gm 5-ASA enemas will maintain remission in 90% of patients.

Oral 5-ASA Agents

A motto in our clinic is "make friends not enemas." Fortunately, a number of oral 5-ASA preparations are currently under development for use in the United States. Claversal (SKB) and Asacol (Norwich Eaton) are 5-ASA tablets that are coated with an acrylic resin. The Claversal preparation breaks down in the ileum in a pH-dependent manner (pH > 6), the Asacol more distally in the terminal ileum at pH 7. Pentasa (Marion) is a sustained-release preparation of 5-ASA incorporated into ethylcellulose microgranules, which act as a semipermeable membrane gradually releasing 5-ASA in a time-dependent and pH-dependent manner throughout the digestive tract. In addition, azo-bond prodrugs deliver 5-ASA into the colon in a manner similar to sulfasalazine. Olsalazine (Dipentum, Pharmacia) is an azo-linked dimer of two 5-ASA molecules attached by the same bond present in sulfasalazine (Table).

TABLE

Release Profiles of 5-Aminosalicylic Acid (Mesalamine) Preparations

	Stomach	Jejunum	Ileum	Colon
Pentasa	—	—	—	—
Claversal/Salofalk			—	—
Asacol			—	—
Sulfasalazine				—
Olsalazine				—
Balsalazide				—

Most of the single 5-ASA compounds rely on the pH of the gut to break down an external coating. Unfortunately, the pH of the gut has not been extensively tested on patients with inflammatory bowel disease. A pH profile from normal individuals may not apply to patients with ulcerative colitis or Crohn's disease, that is, in the presence of inflammation, malabsorption, additional medical therapies, intestinal resection, alterations in transit time or bacterial overgrowth. All of these factors may affect the intestinal pH and may account for differences in absorption and excretion profiles for the different 5-ASA compounds.

Furthermore, it is important to understand how 5-ASA is metabolized. In an unprotected form, 5-ASA is rapidly absorbed from the proximal gastrointestinal tract. The great preponderance of 5-ASA is acetylated within the intestinal epithelium after crossing the epithelial cell, and some may be secreted back into the lumen. Absorbed 5-ASA is primarily excreted in the acetylated form via the kidney. Most of 5-ASA in the bloodstream is in the acetylated form, as the small amounts that bypass epithelial acetylation are acetylated in the liver. Hence, any preparation of 5-ASA that releases into the small bowel is likely to be absorbed to a greater extent than a distally released compound.

When delivered into the colon, 5-ASA is metabolized similarly to sulfasalazine. Some is absorbed, acetylated by the epithelial cell, and excreted by the kidneys. Colonic bacteria also acetylate 5-ASA; however, acetylated 5-ASA is not absorbed by the epithelium and is excreted within the feces. Hence, the advantage of colonic delivery is the availability of 5-ASA for colonic inflammation and reduced absorption into the systemic circulation.

It is not certain which form of 5-ASA is active in the tissues. Acetylated 5-ASA does have some of the same antiinflammatory properties as natant 5-ASA; however, acetylated 5-ASA is not absorbed.

Clinical Trials. In a randomized, placebo-controlled study performed at The Mount Sinai Hospital by Samuel Meyers and other members of the faculty, Dipentum was used in a dose-ranging study for a small number of patients with ulcerative colitis who were intolerant of sulfasalazine. Although there was an apparent dose effect between 0.75 gm and 3 gm in acute ulcerative colitis, the sample sizes were insufficient to demonstrate a statistical dose effect. Further studies will be necessary to define the optimal dosing schedule of olsalazine in acute ulcerative colitis.

In maintenance studies performed abroad, olsalazine has been well tolerated by 80% of patients who could not tolerate sulfasalazine. There is 20% cross-reactivity with similar intolerance to sulfasalazine and there is a unique form of diarrhea associated with olsalazine due to small-intestine (and possibly colonic) secretion of bicarbonate. The secretion does not occur in usual doses of 5-ASA, but has been clearly demonstrated in patients treated with olsalazine. The diarrhea is dependent on the extent and severity of colonic inflammation. The diarrhea also correlates to the degree of azo-bond splitting of the olsalazine molecule. One might expect more problems with diarrhea in patients with severe colitis, although, as the colon heals, it is able to adapt to the increased fluid load. One might also anticipate that olsalazine should be introduced in gradually upward-titrating doses to allow the colon to adapt to increased fluid load.

Other 5-ASA compounds being developed in the United States include Asacol (ASA to the colon), which was developed to deliver the same active ingredient of sulfasalazine into the colon in a manner similar to sulfasalazine. Asacol was initially studied in Europe in maintenance trials, which showed a therapeutic equivalency to sulfasalazine. However, when Asacol was tested in the United States at the Mayo Clinic in patients with active ulcerative colitis, a dose-ranging study demonstrated superiority of 4.8 gm (equal to 12 gm of 5-ASA from sulfasalazine) compared to placebo. However, in a small group of patients randomized to 1.6 gm of Asacol (equal to 5-ASA from 4 gm of sulfasalazine), no statistical superiority over placebo was identified. This was a setback in the eyes of the Food and Drug Administration (FDA) because of the pharmaceutical company's approach, introducing Asacol as an "old drug" rather than a new entity. The FDA has requested evidence for therapeutic *equivalency* to sulfasalazine at *equal* doses, or *safety* data at the *higher* doses needed to prove efficacy. We anticipate a resubmission of Asacol with new data in the near future.

Another compound actively being studied in the United States is Pentasa, which delivers 5-ASA in a sustained-release preparation, delivering approximately 50% of the drug into the small intestine and the other half into the colon. One must not assume that, because half is delivered into the small intestine, 50% of the 5-ASA is absorbed. As the 5-ASA is released from the ethylcellulose granules, some of it may be acetylated within the lumen and, hence, less actively absorbed. Thus, in absorption studies, the absorbed proportion of all of the different 5-ASA compounds appear fairly equal, albeit with a large intra- and inter-patient variability. The single component agents (Asacol, Pentasa, and Claversal) have relatively similar profiles of urinary excretion, whereas the azo-bond preparations (olsalazine and sulfasalazine) have a lower systemic absorption of 5-ASA.

Studies comparing Pentasa and sulfasalazine in equimolar doses of 5-ASA performed in Europe demonstrate therapeutic equivalency for the maintenance of remission in ulcerative colitis. In a multicenter, placebo-controlled, dose-ranging study of Pentasa performed in the United States and presented at Digestive Disease Week, in May 1990, the 2-gm and 4-gm daily doses were superior to placebo and to 1 gm at inducing remission of active ulcerative colitis over eight weeks. Again, there was a prominent placebo response, as Janowitz has documented. However, one of the difficulties demonstrated in this large 400-patient study was the discrimination between doses. The 4-gm dose demonstrated numerical but not statistical superiority compared to the 2-gm dose for clinical improvement, with statistically significant improvement noted only in the histologic changes. Unfortunately, the diversity between patients did not allow sufficient statistical power to discriminate between different doses, so it remains to be determined whether the 4-gm or 2-gm dose should be prescribed initially. It is to be hoped that a second, 300-patient trial will discriminate between the 2-gm and 4-gm doses.

We have also submitted the results of a multicenter, placebo-controlled, dose-ranging study of Pentasa in Crohn's disease to the 1990 Digestive Disease Week. This study has demonstrated superiority of the 4-gm dose in mild to moderately active Crohn's disease, independent of disease location. There does appear to be a difference in dose response between patients with Crohn's disease and those with ulcerative colitis and, as one might expect, the deeper, transmural inflammation of Crohn's disease probably requires higher doses than the superficial inflammatory process of ulcerative colitis.

What separates the 5-ASA agents is a different profile of release: Pentasa provides sustained release of 5-ASA through the small intestine and colon, which might be more effective for Crohn's disease in the small intestine; Asacol and Claversal release somewhat more distally in the small intestine; and the azo-bond products release 5-ASA directly into the colon.

Thus one must consider the advantages and disadvantages of proximal versus distal release. 5-ASA delivered to the small intestine will enhance the potential of ileal and right colonic antiinflammatory properties, at the expense of increased absorption and some potential for nephrotoxicity. These drugs are salicylates, and in animal studies there has been evidence of salicylate-induced interstitial nephritis. However, blood levels of 5-ASA sufficient to induce changes of interstitial nephritis are an order of magnitude higher than those achieved in humans. Nevertheless, there is concern for nephrotoxicity over the long run when patients are treated for many years, especially if there is preexistent kidney disease or 5-ASA is used in conjunction with other nonsteroidal antiinflammatory drugs.

In addition to reducing systemic absorption, proximal release of 5-ASA will prevent more distal delivery but, interestingly, this has not been a problem in clinical trials, as exemplified by the Pentasa studies in ulcerative colitis in which half of the drug has been released into the small intestine. Therapeutic equivalence with sulfasalazine has still been demonstrated. On the other hand, distal release will improve colonic delivery of 5-ASA and reduce systemic absorption, but the drug will not be available in the small intestine for therapy of Crohn's disease.

As far as safety is concerned, postmarketing surveys of 5-ASA have demonstrated side effects in approximately 3% of patients. In controlled clinical trials, approximately 15% of patients note side effects related to 5-ASA, a frequency which is equal to or lower than for placebo-treated patients. For sulfasalazine, 25% to 30% of patients report adverse effects in controlled trials. The 5-ASA compounds have been tolerated by 80% of patients who cannot tolerate sulfasalazine, but a small percentage of patients will report the same side effects with 5-ASA as with sulfasalazine. One specific side effect from sulfasalazine that may be related to the 5-ASA component is "toxic colitis." Virtually 100% of patients with worsening of diarrhea with sulfasalazine will have the same effect with 5-ASA. This must be differentiated from the secretory diarrhea noted with olsalazine, which occurs as an increase in watery diarrhea at the initiation of therapy. The incidence of watery diarrhea with olsalazine is on the order of 6% to 15% and probably can be avoided by gradual titration of the dose at the point of introduction of olsalazine therapy.

The advantages of 5-ASA are the ability to provide higher doses as well as the potential for targeting therapy to specific sites of inflammation with reduced adverse effects. The disadvantages of 5-ASA therapy are minimal; it appears to have efficacy equal to sulfasalazine when delivered orally and superior when delivered in a topical form (enema), and to markedly improve the side-effect profile.

The New Steroids:

Can There Be Potency without Toxicity?

David B. Sachar, M.D.

Obviously, it would be an ideal goal, not just for ileitis and colitis, but also for pharmacology in general, to have a sort of magic bullet, to have a drug that was potent and effective, therapeutic and beneficial, but that did not have any side effects. The ideal magic bullet would certainly be a corticosteroid that has the antiinflammatory activity of the glucocorticoids without the long unhappy catalogue of adverse effects with which we are all familiar.

The antiinflammatory actions of the corticosteroids include decrease in capillary permeability, reduction of chemotaxis, stabilization of lysosomes, inhibition of cellular immunity, and inhibition of prostaglandin metabolism.

In order to exert all these actions, the corticosteroid must bind to the glucocorticoid receptor. In fact, the antiinflammatory activity of corticosteroids, as we understand it, is strictly dependent on their affinity for the glucocorticoid receptor. That affinity depends on four "sacred" sites on the molecule, exemplified by hydrocortisone (Fig. 1): the 4,5 double bond, the 3-keto, the 20-keto, and the 11-hydroxy. Cortisone, as produced by the adrenal cortex, has a keto at the 11 position instead of the hydroxy. But in order to have antiinflammatory glucocorticoid capability, the molecule has to be activated by liver metabolism to hydrocortisone, the 11-hydroxy form.

The 1950s: Synthetic Improvements to Reduce Mineralocorticoid Activity. In the 1950s, with the beginning effort to produce synthetic improvements on the corticosteroid molecule, the first effort was to preserve the glucocorticoid antiinflammatory activity but to reduce mineralocorticoid activity. That was done by introducing the 1,2 double bond to create prednisolone (Fig. 2), which preserved the same glucocorticoid and antiinflammatory activity as hydrocortisone, but which had less mineralocorticoid activity. Now, in the United States we use a lot of prednisone, again a keto at the 11 position instead of the hydroxy, but only with activation in the liver does prednisone become converted to an active form, prednisolone, which is why prednisolone is a favored drug with our colleagues in England, and which is why prednisone is useless as a topical agent. All the topical enemas that use prednisone-like agents must use prednisolone, because the molecule must have the 11-hydroxy, one of the four "sacred" sites, in order to be active.

The 1960s: Increasing Systemic Potency. In the 1960s, the next step was to increase the systemic potency of these agents. That goal was achieved by inhibiting the biodegradation of the molecule. Specifically, an introduction at the 9 position of a halogen inhibits binding to transcortin and in that way slows down biological degradation and keeps the systemic levels high. With the introduction of a fluoride at the 9 position, prednisolone becomes triamcinolone (Fig. 3). With the introduction of a 9-chloride, we have beclomethasone. This inhibition of biodegradation provides increased systemic potency, but not increased *topical* potency, because all that the 9-halogenation is doing is slowing down *systemic* metabolism by inhibiting transcortin binding.

Adapted from the author's presentation at the seminar "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" held at The Mount Sinai Medical Center, December 8, 1989. From the Department of Gastroenterology, Mount Sinai Medical Center. Address reprint requests to David B. Sachar, M.D., Box 1069, One Gustave L. Levy Place, New York, NY 10029-6574.

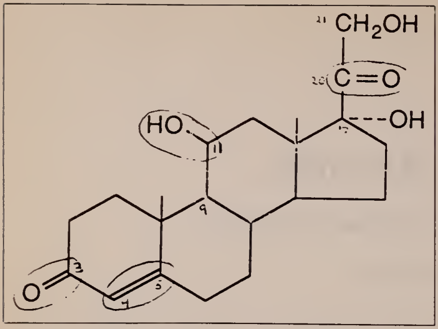
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Fig. 1. Hydrocortisone.

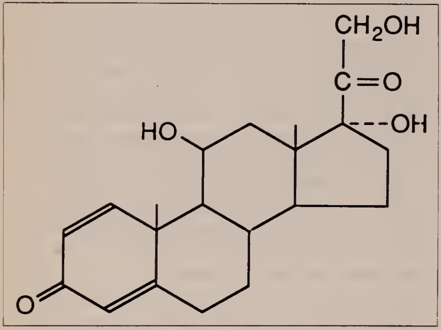
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Fig. 2. Prednisolone.

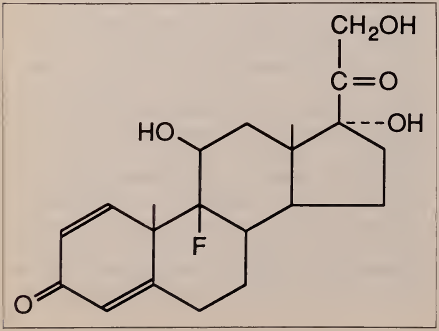
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Fig. 3. Triamcinolone.

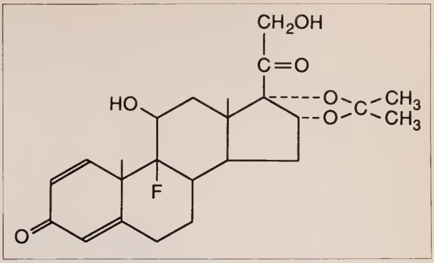

Fig. 4. Triamcinolone acetonide.

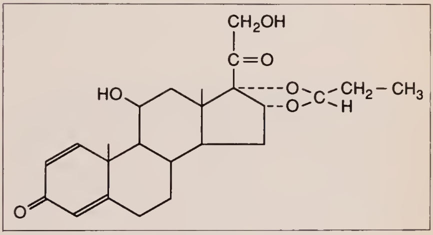

Fig. 5. Budesonide.

The 1970s: Creating More Topically Active Agents. In the 1970s, there was an interest in getting more topically active agents. This goal was achieved by introducing different sidechains. One example is triamcinolone acetonide (Fig. 4). Similar efforts to get better topical action by more affinity for topical sites resulted in the development of betamethasone valerate, beclomethasone dipropionate, and so on. In the sidechain resides the increased topical potency.

The 1980s: "Supertopical" Agents. Most recently, within the last decade, there has been an effort to make "supertopical" agents. These are agents in which further changes in the sidechains at the 17 and 21 positions have resulted in increased tissue binding, increased glucocorticoid receptor affinity, and hence even more topical potency. One example is budesonide (Fig. 5), which has a sidechain that increases tissue binding and increases glucocorticoid receptor affinity, so that it achieves approximately 15 times the potency of prednisolone and is at least 100 times more potent than hydrocortisone. Similar principles underlie the development of fluticasone propionate and tixocortol pivalate.

In addition to increasing topical effectiveness by manipulation of the sidechain, one other change has been made: the 9-halogen has been removed. That simple modification takes the brakes off the biodegradation process and once again allows this highly topically active agent to be very rapidly metabolized. Our aim, after all, is to avoid systemic potency; we are looking for topical potency and rapid systemic clearing. The removal of the 9-fluoride allows increased biotransformation and much less systemic effect. One-pass degradation occurs as the compound goes through the liver, because of its rapid binding to transcortin.

For the 1990s. Some of these agents have been useful for topical action on the bronchial mucosa, as in the treatment of asthma. The hope, the dream for the 1990s would be to develop similar analogues that in the gastrointestinal tract have the topical therapeutic efficacy of the corticosteroids without the systemic toxicity.

Having heard about the theoretical basis for the new nonsystemically active steroids, we next want to learn how well they work in clinical experience. To lead this discussion about clinical experience with the new steroids, we were very fortunate to have Dr. Derek Jewell come from Oxford. The challenge, though, in inviting Dr. Jewell to participate in our symposium, was trying to figure out what to ask him to discuss since he could expertly deal with any aspect of our program. He is a brilliant immunologist, clinician, clinical investigator, and an administrator as well, currently serving as Scientific Secretary of the International Organization for the Study of Inflammatory Bowel Disease.—DBS

The New Steroids:

Clinical Experience in Ulcerative Colitis

DEREK P. JEWELL, M.A., D.PHIL., FRCP

SINCE the demonstration in 1955 that cortisone was an effective treatment for active ulcerative colitis, the management of the disease has had a dramatic effect on the mortality. Thus, the mortality of a severe attack of the disease in Oxford prior to 1952 was about 35%. Since then it has progressively declined to a current figure of less than 1%, which includes patients coming to urgent surgery. This, of course, reflects better understanding of fluid balance, nutrition, and surgical intervention, as well as the use of corticosteroids. However, the side effects of the steroid drugs are well known and, although few serious adverse reactions occur in most of our patients with ulcerative colitis, patients are often reluctant to take them. Hence, new steroid compounds that have low systemic bioavailability have been developed. This property can be conferred by poor absorption, by complete first-pass metabolism in the liver, or by a mixture of both. Such steroids should allow large doses to be given without risking serious side effects.

Some of these newer steroid molecules have been used for some years (listed in the Table as "established"). More recently, three new compounds have been subjected to clinical trial and this discussion concentrates mostly on those newer compounds.

Beclomethasone Dipropionate. This compound was shown by a Canadian group to have minimal effect on the hypothalamic-pituitary-adrenal axis when given as a retention enema (1). Furthermore, it appeared to be effective for active, distal ulcerative colitis, but a placebo-controlled study has not been performed. This preparation has not come into widespread use.

Betamethasone-17-Valerate. This preparation, when given as a retention enema, causes less reduction in serum cortisol concentrations than a prednisolone enema, which indicates its low systemic bioavailability. In a trial of 5 mg daily compared with a prednisolone retention enema (20 mg), both compounds appeared equally effective in patients with active ulcerative colitis over a four-week period (2). Betamethasone administered by rectum seems as effective as beclomethasone when tested in an open study as well as in a formal double-blind study (1, 3).

Betamethasone enemas, therefore, seem a satisfactory preparation for the management of active distal disease, but they are not in general use in the United States or the United Kingdom.

Prednisolone Metasulfobenzoate. This steroid seems to be absorbed from the rectum but is cleared by first-pass metabolism such that only 6% of a rectally administered dose appears in the blood (4). This is considerably less than with prednisolone 21-phosphate. It appears to have similar efficacy to prednisolone used topically, as shown by a trial reported from St. Mark's Hospital (5). This study compared an enema of prednisolone metasulfobenzoate with an enema of prednisolone 21-phosphate (20 mg) given daily for four weeks to 40 patients with active distal ulcer-

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Adapted from the author's presentation at the seminar "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" held at the Mount Sinai Medical Center on December 8, 1989. From the Gastroenterology Unit, Radcliffe Infirmary, Oxford. Address reprint requests to the author, who is Consultant Physician, Gastroenterology Unit, Radcliffe Infirmary, Oxford, England OX2 6HE.

TABLE

Steroid Compounds with Poor Systemic Bioavailability

Established	New
Beclomethasone dipropionate	Tixocortol pivalate
Betamethasone	Budesonide
Prednisolone metasulfobenzoate	Fluticasone

ative colitis randomized to receive one or the other treatment. Although the number of patients was small, there was no difference in the response to the two preparations whether assessed clinically or sigmoidoscopically (Fig. 1). Thus, prednisolone metasulfobenzoate is an effective preparation with low systemic bioavailability, and it is now in common use in the United Kingdom. Interestingly, it has recently been introduced as a foam preparation, but this gives serum steroid concentrations similar to those with equivalent doses of prednisolone (6). Further studies are awaited.

Tixocortol pivalate. Tixocortol is derived from cortisol, the 21-hydroxyl group on ring D of cortisol being replaced with a thiol group esterified with pivalic acid. It is absorbed from the intestine but is cleared by first-pass metabolism and has been shown to have no effect on plasma cortisol. Since it is absorbed, it can only be used as a retention enema but, in this form, it is equally as effective as betamethasone enemas, although these studies performed in France, have not been fully published.

In the United States, Stephen Hanauer of the University of Chicago reported on three trials comparing the effects of 250 mg tixocortol when given as an enema with 100 mg of hydrocortisone, also as an enema, in patients with active, left-sided colitis (7). Patients were receiving sulfasalazine on entry into the trial, and this was continued, but no patient was receiving oral or topical corticosteroids at entry. The duration of the trial was three weeks. Combining the three trials, a total of 337 patients were entered. About 68% of patients improved on tixocortol compared with a similar proportion (75%) receiving hydrocortisone—not a significant difference.

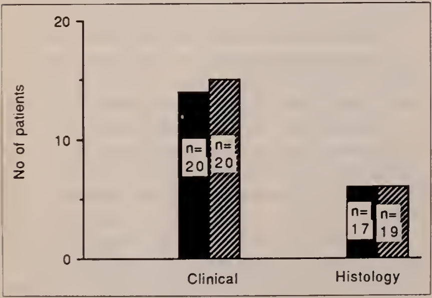

Fig. 1. Number of patients showing clinical and histological improvement following two weeks' treatment with retention enemas of prednisolone 21-phosphate (black column) or prednisolone metasulfobenzoate (hatched column). Drawn from the data of McIntyre et al 1985.

Thus, tixocortol is an effective steroid for topical use in ulcerative colitis and is not associated with adverse reactions.

A further study has been performed to determine the optimal dose of tixocortol. Small numbers of patients were treated with 250 mg, 500 mg, or 100 mg of the drug in enema form. There appears to be no dose-response, 250 mg achieving the maximal effect.

No formal study has been performed with an oral preparation but, from its pharmacokinetics, tixocortol is unlikely to provide high concentrations in the colonic lumen when given by mouth.

Budesonide. Studies with this new steroid are limited. In common with all the newest steroid compounds, it is not water soluble, which has caused considerable problems in formulation. One trial with budesonide has been published from Sweden (8). A retention enema of budesonide (200 mg/100 mL) was compared with a prednisolone phosphate enema in patients with left-sided ulcerative colitis in relapse. Sixty-four patients were randomized into the study and were continued on one or the other treatment for four weeks. In terms of clinical response (reduction in urgency, bleeding, stool frequency) both drugs were equally effective and no adverse reactions were reported. Sigmoidoscopically, 52% given budesonide improved, which was significantly better than the 24% improving in the prednisolone group. A similar difference was seen histologically.

Therefore, budesonide looks promising, and further trials are in progress with enema and oral preparations.

Fluticasone. This latest steroid differs from the others discussed because it is poorly absorbed. We have performed a study in Oxford in which patients with well-established ileostomies were given a single oral dose of fluticasone; subsequently the effluent was collected. From 45% to 97% of the oral dose was recovered in the ileostomy effluent, with a mean of 70% (J Snook and DP Jewell, unpublished observations).

On the basis of this result, a double-blind, randomized control of oral fluticasone (20 mg daily) against placebo was performed in patients with active, left-sided ulcerative colitis (P Angus and DP Jewell; in preparation). The trial period was for four weeks, and 59 patients of 60 entered were evaluable. The response of the fluticasone group was no different from that of the placebo group, whether assessed clinically, sigmoidoscopically, or histologically (Fig. 2). Six of 30 patients treated with fluticasone were withdrawn from the trial because of worsening symptoms, compared with three in the placebo group. This result was disappointing, especially since fluticasone is effective in the bronchial tree when given topically. It is possible that the remarkably good response to the placebo may have confounded the result! A large multicenter trial of fluticasone versus prednisolone has recently been completed in the United Kingdom, and the results are awaited with great interest.

Conclusion. All the new steroids developed to provide low systemic bioavailability appear to have met this objective. With the exception of fluticasone, they achieve this aim largely by first-pass metabolism through the liver. This limits their use to topical administration into the colon, but when used as a retention enema for active ulcerative colitis they are as effective as hydrocortisone or prednisolone. Fluticasone is both poorly absorbed and rapidly cleared by the liver and so has only been used as an oral preparation. Unfortunately, the only trial available at the moment suggests that it is no better than placebo.

Questions and Answers

Sachar: I would suggest to our colleagues in the pharmaceutical industry that they find out what was in the placebo used for the fluticasone trial and then patent it!

Hanauer: Someone is going to ask why tixocortol is not available in the USA. It seems unlikely that it will be available because of formulation problems and major difficulties persuading the FDA that it is genuinely active therapeutically.

Sachar: Is it not curious that patients do so well by themselves? It creates major problems in trying to establish the efficacy of new agents.

Jewell: The high placebo response is certainly a confounding factor. In the fluticasone trial, two factors may be relevant. Firstly, as it was a placebo-controlled study, only patients with mild attacks (less than 5 bowel actions daily) were entered, and it is probable that the spontaneous remission rate is higher in this group than in patients with more severe attacks. Secondly, the trial was limited to patients with disease not extending beyond the splenic flexure. Thus, a considerable proportion (about 30%–35%) had disease limited to the rectum. Although the proportion was similar in each treatment group, the well-known resistance of proctitis to any form of medical therapy might have prejudiced the overall result. Nevertheless, if the analysis was restricted to patients with more extensive disease, fluticasone did not look any better than placebo.

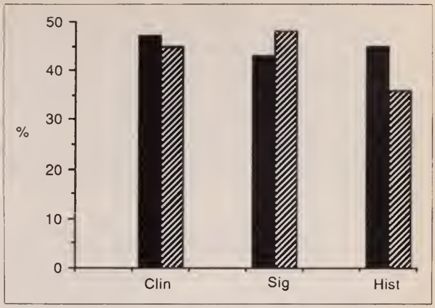

Fig. 2. Percentage improvement of patients after four weeks' treatment of fluticasone (black column) or placebo (hatched column) as assessed clinically, sigmoidoscopically, or histologically.

Sachar: The only real difference between the placebo and active groups in their prestudy characteristics was the sex distribution, with many more men in one group and many more women in the other group. Does that make any difference at all with regard to therapeutic response or resistance to therapy of distal proctitis? Is there a sex difference?

Jewell: It's a good question. We've actually looked at that. We don't think there is clinically, but I have actually looked back at all the enema studies that have ever been done, either with steroids or 5-ASA, and I don't see any sex difference coming up. I think that was just a chance thing that happened.

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Another way of avoiding the systemic toxicity of steroids, besides designing new steroids, is not to use steroids at all but to use something else instead. That something else is often antimetabolites, as we have learned largely through the pioneering efforts of Dr. Burton Korelitz. Dr. Korelitz is the role model of a clinical scholar. Although he has a vast clinical experience, so do a lot of other people. What particularly distinguishes Burt Korelitz is the way that he has mined this clinical experience as a resource for indefatigable clinical investigation. Foremost among his many accomplishments is his long-term experience with antimetabolites in inflammatory bowel disease.—DBS

Antimetabolites in Inflammatory Bowel Disease:

Long-Term Experience

Burton I. Korelitz, M.D.

THE MODERN era of immunosuppressive therapy in inflammatory bowel disease can probably be attributed to Hitchings and Eliom, who introduced azathioprine to prevent renal transplant rejection through their work at Burroughs-Wellcome. They received the Nobel Prize a year ago. Why should their findings have been of such importance to gastroenterologists back in the 1960s? In that era many diseases of unknown cause were considered autoimmune. Therefore, we gastroenterologists reasoned that if a drug like azathioprine could be used for transplant patients, why not use it for other autoimmune situations?

The medical literature before 1973 showed a mean success rate of 72% in sick people with Crohn's disease. This was almost consistently true in uncontrolled studies. Everyone who tried azathioprine therapy found some degree of success, starting with Brian Brooke, who reported that near-terminal patients had fistulas that were closing as a result of the therapy (1).

The results of controlled trials thereafter were not as good. However, in every study there were extenuating circumstances: the duration of therapy was not long enough, those who did not come to surgery were slightly more numerous than those who did, patients had subjective improvement without remission. The conclusions of those many studies, culminating in the largest of all, the National Cooperative Crohn's Disease Study, served to virtually eliminate any role for azathioprine as a treatment for Crohn's disease (2). Subsequently, we retrospectively showed many errors made in interpretation of the data compiled by the National Cooperative Crohn's Disease Study (3).

Results of 6-MP Therapy

Crohn's Disease. In the late 1960s, coincident with the national study, Daniel Present, David Sachar, Henry Janowitz, and I launched a double-blind controlled study of 6-mercaptopurine (6-MP) treatment in inflammatory bowel disease. We chose Crohn's disease rather than ulcerative colitis, even though my favorable earlier experience had been with the latter. The resulting data was conclusive; 6-MP therapy in the sickest patients with Crohn's disease who had failed other drug treatments, including steroids and sulfasalazine, was effective (4). Out of 39 patients, 26 responded to 6-MP, as opposed to 3 out of 39 responding to placebo, a highly statistically significant response (Table 1).

The study led us to conclude that the drug was effective, that it permitted elimination or at least marked reduction of steroids; moreover, it was the first drug demonstrated to show closing of fistulas. The mean response time was 3.1 months, but we have learned subsequently that 6-MP can be very effective even when the re-

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Adapted from the author's presentation at the seminar "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" held at The Mount Sinai Medical Center, December 8, 1989. From the Department of Medicine, Lenox Hill Hospital. Address reprint requests to the author at 100 E 77 Street, New York, NY 10021.

TABLE 1
Results in 39 Crossover Patients

Treatment	Improved*	Not improved
6-MP	26/39	13/39
Placebo	3/39	36/39

Adapted from Present DH, et al (ref 4).
* Whereas 67% of patients improved with 6-MP, only 8% improved with placebo. The difference is 59% with 95% confidence limits of 32% to 86% ($P < 0.0001$).

sponse is delayed for 6 months to a year. Therefore, ACTH and corticosteroids often must be used to buy time in which the 6-MP has a chance to work. However, our subsequent observations show that the response to 6-MP is not dependent on the coincident steroid therapy.

In addition to 6-MP closing fistulas, we learned that it worked better when there was colonic involvement with Crohn's disease rather than ileitis; this is particularly important because in Crohn's disease, the most common distribution is ileocolitis. At the Cleveland Clinic, 92% of Crohn's disease patients have come to surgery, the most common distribution was ileocolitis, and the most common indication for operating on the patients with colitis was fistulas (5). Therefore, it is clear that 6-MP could have significantly altered that outcome.

Recent Observations in Inflammatory Bowel Disease. Subsequently, Adler and I have reviewed my later experience with 6-MP in 152 patients with Crohn's disease; we found that in 71%, steroids could be eliminated, and in 64%, fistulas healed (6) (Table 2). Furthermore, there was 64% success in healing perirectal abscesses and fistulas, a goal for which drug therapy has been the least effective; 6-MP has been at least as effective as metronidazole for this purpose, and with less toxicity.

TABLE 2
Results of 6-MP in Crohn's Disease

Still better than earlier (70%).	
Favorable reports from other centers.	
Indications for 6 MP in Crohn's disease with best results:	
Eliminations of steroids	71.4%
Healing internal fistulas	64.1%
Healing perirectal abscesses	64.6%
Healing recurrent ileitis	80.0%
Healing Crohn's disease of stomach and duodenum	100%
Permitting elective resection	100%
Prophylaxis against recurrence	?

Adapted from Adler DJ, Korelitz BI (ref 6).

Even though one of the weakest indications was recurrent small-bowel obstruction, since irreversible fibrosis might be just as responsible as reversible inflammation, if the initial obstruction could be reversed, 6-MP was effective in 45% in preventing future attacks of obstruction. We found that 6-MP could eliminate abdominal masses which were mostly inflammatory, heal recurrent ileitis in the ileostomy in a large percentage, and so far has healed all 3 patients with Crohn's disease of the stomach and duodenum—cases in which until now gastroduodenal surgery has been required, yet provided only temporary relief. The agent 6-MP has served to permit elective resection in patients with extensive Crohn's disease earlier considered inoperable; coincident with response to immunosuppressive therapy, the margins of the inflammatory process become better defined, so that definitive surgery can be performed and quality of life improved. I have also used 6-MP prophylactically after resection. The value of azathioprine for maintenance of remission has been shown by O'Donaghue et al (7) and has been supported by our own data on 6-MP. Earlier I was using it prophylactically after two resections; now, in the most severely affected patients, I am using it even after the first resection.

The time until elimination of steroids after starting treatment with 6-MP has been a mean of 3.4 months. But, as I've said, in some patients it takes much longer and is still effective. The duration without steroids while on 6-MP in this most recent analysis has been a mean of 2.9 years, and the duration of remission after stopping 6-MP, 15 months before disease activation recurs.

A patient who had Crohn's disease of the ileum who did not accept a recommendation for prophylactic 6-MP following an extensive resection developed recurrent ileitis proximal to the anastomosis. He then did begin therapy with 6-MP, and when the X-rays of the small bowel were repeated, all signs of the disease had disappeared (Fig.).

Ulcerative Colitis. What about ulcerative colitis? A review of the medical literature before 1973 showed a still better response rate, 80%, than in Crohn's disease. Again most of the uncontrolled trials showed good results, but the controlled studies, for reasons similar to those in Crohn's disease, were not as good. In Daniel Present's experience with 6-MP in ulcerative colitis, there were 2+ and 3+ responses in 73% and thereafter continued well-being either with or without 6-MP therapy in 64%.

Adler and I have looked at our patients with ulcerative colitis treated with 6-MP, and we

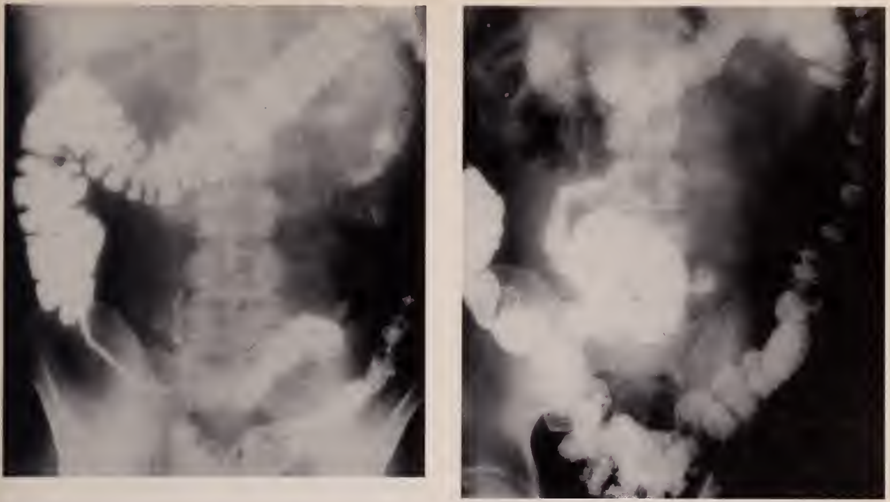

Fig. **Left** Recurrent ileitis after ileocolic resection. **Right** Same patient after treatment with 6-MP for a year.

found a 48% success rate, with a mean steroid-free period of 19 months (8). When we added to this series a few more patients whose corticosteroid dosage could be reduced but not eliminated, the favorable response rate increased to 61%. These results were not as good as in Crohn's disease. Still, we had chosen only the sickest patients who had failed all other forms of drug therapy and were not yet absolute candidates for colectomy.

We did find that the mean time to response to 6-MP was 2.5 months, shorter than in Crohn's disease. In long-term follow-up, these patients were able to maintain steroid-free remissions for a mean period of 21 months after the end of 6-MP therapy.

Toxicity of 6-MP in Inflammatory Bowel Disease

The advantages of 6-MP are the avoidance of the complications of steroids, tolerance by most patients without side effects, and prophylactic value. It is the first drug shown to have prophylactic value against recurrence of Crohn's disease.

But what about the disadvantages? The biggest one has been fear—not only the fear of patients, but also the fear of doctors who have not had experience with it and who have associated the drug with cancer. As John Singleton once said, if a drug is used in the treatment of cancer, people are going to be afraid that it also causes cancer. We know that 6-MP has caused allergic reactions. We have worried about its role during pregnancy and in children with IBD. It is an inconvenient drug in the sense that the patient resents the careful monitoring which we perform. It can cause infections. And maybe it does cause cancer.

Once Daniel Present and I accumulated a good deal of experience with 6-MP in the treatment of both Crohn's disease and ulcerative colitis, we again joined forces; with the help of Meltzer, Krumholz, and Wolke we set out to define its toxicity in the patients we had treated. We covered the period 1967 to 1985, almost 400 cases, many years of observation, and 90% follow up.

What we found is that complications broke down into those that could be and those that could not be clearly attributable to 6-MP therapy. Those almost certainly attributable to the drug usually occurred early (Table 3).

Pancreatitis. Pancreatitis occurred in 3.3% and in all instances was typical. It happened three weeks or so after the patient had begun taking the drug. In all cases it was reversible when the patient stopped taking the drug, and it recurred in those who were rechallenged. We therefore concluded that we should not use 6-MP once pancreatitis had developed. I have subse-

TABLE 3
Complications Directly Attributable to 6-Mercaptopurine

	No. (%)
Pancreatitis	13 (3.3)
Bone marrow depression	8 (2)
Allergic reactions	8 (2)
Drug hepatitis	3 (0.8)
Mortality	0 (0)
Reversibility	32 (100)

Adapted from Present DH, Meltzer SJ, Krumholz MP, Wolke A, Korelitz BI (ref 9).

quently tried desensitization to 6-MP starting at very small doses, but it did not work. Moreover, cross-reactivity between azathioprine and 6-MP is the rule. Nonetheless, when I have switched to azathioprine and tried desensitization, I have the experience of it being tolerated and being therapeutically effective in 2 patients.

Bone Marrow Depression. In the early years bone marrow depression occurred in 8 patients, or 2%. In all 8 patients the marrow depression reversed and there were no fatalities. For some reason, we are not seeing it any longer, perhaps because of careful monitoring or because therapy begins with a lower dose.

Allergies. Allergic reactions were found in 2%. These included fever and in 2 cases arthritis. Drug hepatitis was rare. It did not occur early, like the other manifestations, and it was reversible once the drug was discontinued, with no sequelae. Altogether there was no mortality in this group and all complications were reversible.

Infections. We recorded a variety of infectious complications that occurred either while the patient was receiving the 6-MP or at some later date after the drug had been stopped (Table 4). One was disseminated cytomegalovirus infection. This we feel was clearly related to the 6-MP because it occurred in a young woman who did not follow directions. When she began to develop a fever she continued to take the drug, although she was supposed to stop taking it immediately. She was in the hospital for 4 months with a perforation of the small bowel complicated by liver abscesses. Each complication, however, was managed and reversed. She survived and has been well ever since as far as the Crohn's disease is concerned. It has been an interesting observation that the more severe the complication of the drug, if the patient survives, Crohn's disease activity seems to "burn out".

TABLE 4
Infectious Complications Observed in 396 Patients with Inflammatory Bowel Disease Taking 6-Mercaptopurine

Complication	No.
Disseminated cytomegalovirus*	1
Liver abscess*	2
Pneumonia	5
Herpes zoster	8
Septic phlebitis	1
Fever of unknown origin†	1
Hepatitis	10
Q fever	1
Total	29‡

* One patient had both cytomegalovirus and a liver abscess.
† This patient is also included in the category for bone marrow depression in Table 1.
‡ Total percentage of patients with complications was 7.4%. No patients died.

Herpes zoster occurred in quite a few patients while they were receiving 6-MP. In some we continued the drug; in others we stopped it. There was only one case of severe herpes zoster with an encephalitis lasting for 2 or 3 days, and fortunately this also was self-limited.

There were a few cases of pneumonia. Most of them were mild and the patients were treated as outpatients. This group included patients who had pneumonia long after discontinuing 6-MP therapy as well as patients still receiving the drug.

There were 2 instances of liver abscesses, including one in the patient with cytomegalovirus infection. The incidence of liver abscesses is higher in patients with Crohn's disease who are not receiving 6-MP than in patients who are receiving the drug.

One young woman developed a fever of unknown origin. She was admitted to the hospital and had a spiking fever for three weeks. A cause was never found. She had mild leukopenia. The fever suddenly defervesced after three weeks and her Crohn's disease then remained in remission for a year.

One patient of Daniel Present's went to Australia while taking 6-MP and came back with a fever of unknown origin; it proved to be Q fever. She too has done very well with the Crohn's disease for what is now 15 to 20 years.

Possible Neoplastic Complications. What about the worst concern of all—cancer? A variety of neoplasms have occurred in our patients both during and after 6-MP therapy (Table 5). One 52-year-old man who had been undergoing 6-MP therapy for about 7 months developed a diffuse histiocytic lymphoma of the brain about a year after the drug therapy stopped. This was the only case of lymphoma. We think it was related to the 6-MP therapy because it is a rare type of tumor,

TABLE 5
Neoplasms Observed in 396 Patients with Inflammatory Bowel Disease Treated with 6-Mercaptopurine

Type of neoplasm	No. of patients
Histiocytic lymphoma, brain	1
Malignant melanoma	1
Islet-cell carcinoma, pancreas	1
Adenocarcinoma, lung	1
Carcinoma, colon	1
Adenomatous polyps, colon	1
Basal-cell carcinoma	2
Prolactinoma	1
Carcinoma, breast	1
Papilloma, bladder	1
Follicular adenoma, thyroid	1
Total	12*

* Total number of patients with neoplasms comprised 3.1% of the study population.

and only in the literature on transplantation do we read about occasional brain lymphomas. Since the time of our one case, there has been one additional case of a cerebral lymphoma reported from France in a patient with Crohn's disease treated with 6-MP.

There was a malignant melanoma in a man who had previously been taking 6-MP for his ulcerative colitis. The tumor was resected and he did well for years thereafter.

Other tumors were an islet-cell carcinoma, a carcinoma of the lung, and a carcinoma of the colon; we did not feel that these were related to 6-MP therapy. The carcinoma of the colon almost certainly preceded introduction of 6-MP therapy. The incidence of some extraintestinal neoplasms, as reported by David Sachar and his colleagues, is higher in the Crohn's disease population than in the general population, independent of 6-MP therapy (10).

What about lymphomas complicating immunosuppressive drugs? Data from Kinlin in Scotland showed us the relative risk of lymphomas in antimetabolite-treated renal transplant cases, which was high; in nontransplant cases, such as rheumatoid arthritis patients receiving azathioprine, where it was lower than in transplant cases but still higher than in the general population; and then in Crohn's disease and ulcerative colitis, where no instances of lymphomas were found among 321 cases surveyed (11).

Daniel Present and I have seen 3 lymphomas in approximately 3,000 patients with Crohn's disease. Of the 500 treated with 6-MP, only one had a lymphoma while undergoing therapy. In Greenstein's studies, there were 4 lymphomas in 1,480 cases (12); this same group has now had 9 lymphomas and none of the affected patients was taking 6-MP.

Perhaps of most concern in respect to fear of carcinoma is the known ulcerative colitis model, namely, the increased risk of cancer of the colon in long-standing ulcerative colitis. What has been our experience here? I can recall 16 patients with carcinoma of the colon complicating ulcerative colitis during the past 20 years. Only one of those was taking 6-MP. Daniel Present recalls 18 patients with carcinoma of the colon during this period; one of those was taking the drug. Therefore, 2 out of 34 patients with carcinoma of the colon had received 6-MP.

What about carcinoma of the bowel in Crohn's disease? I can recall 7 cases of carcinoma in Crohn's disease over this period of time; one of the 7 patients was receiving 6-MP. Daniel Present remembers 10 cases of carcinoma of the bowel in Crohn's disease; one of them was taking 6-MP. We have not made any comparisons of cancer incidence between patients who are taking 6-MP and those who are not, but neither published experience nor our clinical impression supports any strong anxiety for a heightened risk on therapy.

Pregnancy. Patients with IBD are young, half are women, and many of them will want to become pregnant. We advise them to avoid pregnancy if it is not a priority; if it is a priority, then I feel the 6-MP should be discontinued. If a patient gets pregnant while taking 6-MP, do we do a therapeutic abortion? I have recommended it, particularly if the patient is young and the opportunity for a future pregnancy is good. But some have refused this advice, gone through with the pregnancy, and done perfectly well. We do not know, of course, if there is any risk to the newborn in future years. There was one male patient whose wife became pregnant while he was taking 6-MP; the child developed a Wilms tumor at age 4. Whether the tumor was related to the 6-MP or not is very problematic. I know that Lennard-Jones's group in England is now continuing azathioprine therapy throughout pregnancy, and all of the deliveries have been successful and without complication (13).

In summary: the incidence of complications is low. The drug is effective, and its complications must be viewed in proportion to what we are dealing with: sick young people whose quality of life is severely compromised.

I raise the question whether safety increases with time, compliance, and experience. I have not seen a patient with bone marrow suppression in years. I have seen only one case of pancreatitis in the last two years. Important infections have been infrequent and easy to treat.

Recommendations for Management

The duration of therapy is still arbitrary. We used to aim for two years of 6-MP therapy when the drug was successful. Many patients are not willing to stop taking 6-MP at the end of two years, however, when it is the first drug to be responsible for a remission. I have learned to compromise by reducing the dose when I feel continued 6-MP therapy is warranted. Some people stop taking the drug out of fear, even if they are doing well, but not so many do so anymore. Some patients who continue taking it have remained in remission for many years.

There are a few general principles for management of patients undergoing therapy with 6-MP. With stability of the white blood cell count, the period between counts can be increased. If the drug is effective, there is no reason to increase the dose. On the other hand, if the drug does not appear to be effective and the goal is not accomplished, the dose should be increased if the blood cell count permits. If reintroducing steroids briefly is indicated, the steroids in turn serve to raise the white blood cell count and buy a little more time to establish a larger dose of 6-MP. Increasing the dose of 6-MP is clearly responsible for achieving remission in some cases.

Cyclosporine is discussed elsewhere in this issue by Simon Lichtiger. It is my own conviction that cyclosporine will serve as a "quick fix" for patients who are seriously ill and refractory to steroids, buying time for 6-MP to be effective.

On the horizon is FK 506, a potent and perhaps still better immunosuppressive drug developed in Japan and being used in transplant cases in Pittsburgh. I hope—we all hope—it will be effective in IBD. Perhaps this too will have its greatest role in conjunction with the other drugs effective against Crohn's disease and ulcerative colitis.

Thank you very much.

Questions and Answers

Sachar: You see what I mean by mining of vast clinical experience for hard data. I think that it's marvelous that Burt Korelitz and Dan Present and their colleagues have gone back to their clinical experience and have produced from it a lot of useful numbers and useful figures. But one set of important numbers was missing: The *denominators* of the cancer-incidence fractions in patients on and off 6-MP.

Korelitz: I'll have them ready for the next symposium. [Laughter.]

Sachar: I predict you'll find no important difference in incidence between the two groups.

Let me now quarrel with one other number, Burt. Actually, it's not the number I'm going to quarrel with; it's the predicate, the verb, when you said that 6-MP *prevented* future obstruction in 45% of cases. You said you had a number of patients who had obstructions, you put them on 6-MP, and you said 45% of them did not get another obstruction during the time you followed them up, and therefore 6-MP prevented recurrent obstruction in 45%. I think you can tell us that, of a certain number of patients who had an obstruction, followed up for a certain amount of time, 55% had another obstruction, 45% didn't. But what can you tell us about how that experience differs from what happens in the natural course of obstructions in Crohn's disease?

Korelitz: I certainly agree with you, David, that this is not a controlled study. It is strictly based on clinical observation. But I know that, as far as small-bowel obstruction is concerned, if the patient does not develop recurrent obstruction for about 8 months, the odds are good that that patient will not have an obstruction thereafter, whatever the medical program. But in any small group of patients, in the first 8 months those taking 6-MP seem to wait out that period far more successfully than those not taking 6-MP. Every time you bring up a new topic, it means I have to go back to work, and again I am going to try to get that together.

Sachar: Of course, I'm not really arguing with Dr. Korelitz. I'm just trying to set the tone to encourage other people to get up and question or challenge.

Oustler: Steven Oustler from Philadelphia. Is there any correlation between the dosing and the number of side effects you see or the duration of therapy and the incidence of side effects? Also, could you comment on the use of 6-MP or azathioprine in children?

Korelitz: There does seem to be correlation with dosing and effectiveness, because, if we start at one dose and it isn't successful, very often I see that when the dose is raised, within a brief time something begins to happen. The toxicity seems to come early, rather than late. If the patient seems to tolerate the drug early, they will probably tolerate it indefinitely.

As far as children are concerned, pediatricians and pediatric gastroenterologists have been the most resistant to immunosuppressives right from the beginning. But, as I see it, that's all changed now, mostly because who after all gets Crohn's disease? Teenagers have the most virulent disease, and they respond the most effectively. Richard Grand realized this and began to look at it. He presented his data two years ago at the AGA. The patients all had successes and no toxicity. Fred Daum at North Shore just presented his data at the American College meeting; the results were similarly encouraging. So I think that the fear of using 6-MP specifically in children as opposed to adults is now gone.

Oustler: I was interested more specifically in the dosing in children.

Korelitz: The answer is the same: we have no reason to vary the dose because of age or severity.

Oustler: How about weight?

Korelitz: No. We used weight to calibrate dose at the time of the double-blind controlled study, but the correlation between dose/weight and effectiveness/toxicity was not good. I start empirically at 50 mg/day, then take it from there.

Speaker: Since 6-MP is a medication that often takes long before evoking a response, do you continue to increase the dose over the initial 50 mg until you see an effect on the white cell count, or do you stay at one dose waiting for a clinical response?

Korelitz: The purpose of monitoring is primarily to watch the white cell count for toxicity. If that count falls, even in the first week, we have to either reduce the dose or stop the therapy, depending on the profundity of the fall in count.

Sachar: You have said you might give up on 6-MP after 6 months if there hasn't been a response. Are you satisfied that you've taken it to maximum benefit and that it really is a failure until you've seen some drop in the white cell count? In other words, will you push it a little more to get a little bigger drop in that count? If the white cell count is running 7000–8000, will you give up on 6-MP on somebody who's never had a white cell count below 7000?

Korelitz: If the patient's white cell count has not fallen and we haven't achieved therapeutic effectiveness, I will push for a bigger dose, not necessarily for leukopenia, but for a bigger dose, but often that will be accompanied by leukopenia. Therapeutic effectiveness does not necessarily require leukopenia, but I would push the 6-MP to leukopenia if the goal of therapy was not otherwise accomplished.

Sachar: To follow up the question about the duration of treatment and when the side effects occur, might we indicate that that to some extent depends on which side effects we're talking about. Allergic reactions, fever, arthralgia, and certainly pancreatitis occur pretty early—within a few weeks. Some of the rarer reactions, like drug hepatitis, might come much farther down the line.

The interesting thing is about leukopenia. The leukopenias might occur in a couple of different groups. There is one group in whom it can catch you unawares and happen anytime, but there is another small group that John Lennard-Jones talks about, where right at the beginning of therapy there is a sudden, drastic, unexpected drop. He speculates that this might have to do with the spontaneous background of xanthine oxidase deficiency in a normal population, and that those who have low xanthine oxidase who don't metabolize the antimetabolite might be particularly prone to a sudden dangerous drop at the initiation.

Korelitz: Well, David, since we initiated the launching at 50 mg of 6-MP a day, I've not seen that at all. I've not seen anything like that since, I would say, the first five or six years of using the drug.

Sachar: But you are careful in the patients taking allopurinol, right?

Korelitz: Oh, am I careful.

Sachar: You're always careful. Dr. Lichtiger?

Lichtiger: I think you may have answered my question. I am a proponent of 6-MP. I use it without hesitation. The safety is simply elucidated in the literature. Why do you get consent?

Korelitz: Well, I think everyone has touched on it in a peripheral way. In recent years our society has become progressively litigious. I didn't go to medical school to spend my time in that manner; I went to become a doctor. I want to spend my time being a doctor. I don't want to be in court every Tuesday and Thursday. The permission form saves my time.

Sachar: Do you really think having a consent is going to make any difference in whether they're going to sue you or not? Lots of luck.

Korelitz: I do believe it might help if a patient with inflammatory bowel disease who happens to be taking 6-MP does badly.

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One field of research often has lessons that are critical for understanding others. This principle is particularly evident in the cross-fertilization between studies of chronic inflammatory bowel disease and research into rheumatic and related inflammatory or autoimmune diseases. It is for this reason that Professor R. G. G. Russell has so much to offer to this symposium. His background is largely in the cellular biology of bone metabolism, but his lessons about immunomodulation in bone and joint disease have fundamental implications for the pathogenetic mechanism of inflammatory bowel disease in general and for the potential therapeutic actions of cyclosporine in particular.—DBS

Immunomodulation in Rheumatic and Related Diseases

R. G. G. Russell, Ph.D., M.D.

It would be very easy for me to feel out of place here, among a group of gastroenterologists, but what interests me is that many of the phenomena described in other articles in this symposium for epithelial cells could be applied to osteoblasts and other skeletal cells.

Immunomodulation in relation to disease states is obviously a vast topic. What I have chosen to do here is to illustrate, using bone and joint disease, some of the mechanistic concepts developed in recent years, in particular the roles of cytokines and growth factors in relation to tissue destruction. I also comment on the mode of action of cyclosporine and how some of the properties of cyclosporine evident in the systems this symposium focuses on may spill over into the diseases that interest all of us.

Recent Concepts of Mechanism in Bone and Joint Disease

In a patient with rheumatoid arthritis, what happens inside the person's joints is much like what goes on inside the gastrointestinal tract: tissue damage that impairs function by destroying cartilage, underlying bone, and surrounding ligaments and tendons. This leads to deformity and an alteration in structure which can be essentially irreversible.

Even a simplistic scheme of pathogenic mechanisms in rheumatoid arthritis reveals the parallels with inflammatory bowel disease. There is the problem of identifying a cause, which is unknown in each condition. There is an aberrant immunological response in the context of particular subsets of class II HLA antigens in both cases. This leads on to the production of the mediators of the changes that are characteristic of the disease process. Certainly, in joint disease the current emphasis is very much on the role of cytokines, such as interleukin-1 and other mediators, and neuropeptides can also be drawn into the pathogenic mechanisms in both situations. In relation to the tissue damage, the groups of mediators are similar: prostaglandins, leukotrienes, oxygen radicals, enzymes (particularly the metalloproteinases, those latent enzymes which become activated and are necessary to destroy, for example, collagen in extracellular matrix). The products of the damaging events may in turn lead to stimulation of further bursts of cytokine production, with further amplification.

In rheumatoid arthritis a number of disease processes are going on, including the loss of articular cartilage and damage to the bone around joints, which is probably mediated to some extent by prostaglandins but is also mediated by cytokines such as interleukin-1 and tumor necrosis factor.

The Cytokine Interleukin-1. Interleukin-1 is alluded to elsewhere in this issue as one of the earliest mediators in mounting the immune re-

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Adapted from the author's presentation at the seminar "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" held at The Mount Sinai Medical Center, December 8, 1989. From the University of Sheffield, England. Address reprint requests to the author, who is Professor of Human Metabolism and Clinical Biochemistry at the University of Sheffield, at Beech Hill Road, Sheffield, England S10 2RX.

sponse. It is therefore potentially important in a number of disease processes. It may share a common role in a number of disease processes, for example in those involving antigen processing and presentation by macrophages, which are one of the main cell types that produce interleukin-1, even though others do as well. Interleukin-1 acts on T cells, particularly the CD4 type, to produce a proliferative response mediated via interleukin-2, and this leads to amplification of the immune response. This is obviously an essential early part of the normal immunologic response, as well as the altered responses occurring in autoimmune states.

Actions of Cyclosporine. One reason for the interest in cyclosporine is that it has a very specific action early on in that response, in that its major if not exclusive site of action within the T cell is to interrupt specifically the transcription of messenger RNA (m-RNA) for a number of key cytokines. The most important event in explaining much of the action of cyclosporine is the inhibition of interleukin-2 production, so that cyclosporine thereby blocks the autocrine growth factor effect of interleukin-2 on T-cells. But there is clear evidence that cyclosporine also shuts off a number of other cytokines, including interleukin-3, which is the multicolony stimulating factor involved in the early stage of hematopoiesis; γ-interferon, which augments the immune response in several ways; and interleukin-4, which is involved in effects on B cells. Note, however, that not all cytokines are affected, and, interestingly, granulocyte macrophage CSF (GM-CSF), at least coming from this source, does not seem to be inhibited by cyclosporine. Some of the other possible effects of cyclosporine are discussed below.

Tumor Necrosis Factor. Interleukin-1 has many similarities in action to another cytokine, tumor necrosis factor (TNF). TNF_{α} is also a monocyte/macrophage product, while TNF_{β} comes from T cells and is sometimes called lymphotoxin. TNFα and β are very similar in many respects. Furthermore, even though both the primary and tertiary structure of tumor necrosis factor differ from those of interleukin-1 they nonetheless share many properties. To draw on an example from the area of connective tissues, both these agents are potent inducers of prostaglandin and of extracellular protease production, and are mitogens for a number of fibroblasts and other connective tissue cell types.

Both interleukin-1 and TNF may well be involved in the early stages of mounting fibrosis responses in relation to tissue injury. The proliferative effects of interleukin-1 and tumor necrosis factor are evident on the osteoblast-like cells, which it is now possible to grow very easily from human bone samples. These mitogenic effects, as with many cytokine effects, may turn out not to be direct, but to be mediated by a second effect of both these factors on the induction of other mitogens, such as platelet-derived growth factor, which may turn out to be the true autocrine growth factor for these cells.

These and other overlapping properties of both these cytokines in relation to disease processes make both cytokines capable of acting as endogenous pyrogens. They are both probably involved in mounting the acute-phase response that leads to changes in erythrocyte sedimentation rate (ESR) and also involve changes in hepatic protein synthesis. They can be cytotoxic for certain tumor and other cell types. They also have an important effect on augmenting prostaglandin production and producing extracellular metalloproteinases, such as collagenase. They are potent inducers of other cytokines. Interleukin-6 is of particular interest because it may be the ultimate mediator of the induction of the acute-phase proteins in the liver. From the particular standpoint of bone and cartilage, they are both potent resorbing agents for bone and cartilage.

One elegant demonstration of this comes from experiments conducted by Brendan Boyce in Mundy's laboratory in San Antonio. They look at the effects of cytokines and growth factors on bone by applying them locally over the skullbone of young rodents and studying the tissue response produced. After a very short exposure to interleukin-1 a massive alteration in bone turnover occurs, with excess resorption, new bone formation, and some fibrosis. Part of this is prostaglandin dependent, because if the animals are given indomethacin, part of that response, but by no means all, is abrogated.

Bone Resorption and Formation. A word about bone remodeling: Bone is a hard tissue, but it's not dead. The major cells responsible for initiating bone turnover are the osteoclasts, which are multinucleate and resorb away the matrix, again using specific extracellular proteases and acid production to dissolve the mineral. After the bone is resorbed, the osteoblasts come in and fill in the gaps. Any imbalance between the resorption and the formation process produces some of the clinical states of altered bone metabolism—either bone loss as in osteoporosis, or excessive bone, as in deposits derived for example from prostatic tumors. Certain other tumors, such as myeloma, are very erosive toward bone. In fact, the study of patients with myeloma and similar bone-destructive states was the stimulus that led to the identification of so many of the now-known cytokines and growth factors as potential resorbing agents in relation to bone.

In the process of identification of factors responsible for bone resorption in cancer, it has been found that many tumor cells produce factors that will cause bone resorption. It is now possible to study both the production of osteoclasts and their activity in isolation, so it is now easy to look directly at the effects of individual factors on bone resorption activity.

There is now an enormous amount of information on the effects of known cytokines and growth factors and other agents on the induction of osteoclasts and their activity. Colony-stimulating factors, interleukin-1, vitamin D metabolites, transforming growth factors, and so on, all have effects on enhancing bone resorption by affecting osteoclast recruitment.

Destruction-Blocking Cytokines. There are counterbalancing cytokines, and this counterbalance is a very important theme. Two in particular are probably involved in many other processes in bone as well: γ-interferon, and β-transforming growth factor, both of which seem to negate the action of interleukin-1 and tumor necrosis factor in connective-tissue destruction. So both γ-interferon and β-transforming growth factor are capable of being protective against destruction of connective tissue.

Interestingly, these cytokines are quite specific in what they will block. Gamma interferon, for instance, will inhibit the action of interleukin-1 and TNF but will not block the bone-destruction action of parathyroid hormone or vitamin D metabolites.

What is perhaps even more interesting—moving to cartilage systems—is that in articular cartilage actually taken from patients, interleukin-1 will stimulate the release of proteoglycan breakdown products, and so is destructive for cartilage. In the presence of γ-interferon that effect of interleukin-1 is blocked. So it is important to think of the cytokines in families, some of which promote destruction and some of which block it.

The way that these cytokines work is still not absolutely certain, but in the case of cartilage the mechanism may be to inhibit the production of the metalloproteinase that destroys proteoglycans.

To summarize some of the effects of γ-interferon within connective tissues: it blocks bone and cartilage production induced by cytokines; it inhibits cellular proliferation; it inhibits collagen synthesis, and may therefore have effects on blocking fibrosis responses. Interestingly, γ-interferon will enhance the expression of class II HLA antigens by bone cells. Just as epithelial cells present antigens, osteoblasts can present antigens and stimulate T cells; the story is equally convincing.

Crosstalk between T Cells and Osteoblasts. Interestingly, when T cells and osteoblasts are mixed together, there is large stimulation of what is called osteoclast activating factor activity. The most potent of the factors that seems to be responsible for this effect turns out to be TNF_α, which is in fact an osteoblast product, not a T-cell product. So this crosstalk between T cells and osteoblasts involves cytokines coming not just from T cells but from the osteoblasts themselves.

These types of phenomena are probably very important in some of the critical physiological regulatory mechanisms that have to take place in the skeleton, for example the need to balance bone destruction and bone formation tightly in order to maintain the skeleton in an intact state during remodeling. It is thought that this so-called coupling between resorption and formation may involve soluble messages of this type actually being released, say, during resorption, and acting on osteoblasts. One candidate for this is TGF_β, which is present in vast amounts in latent form in bone matrix. When osteoclasts resorb bone, by producing local acid, they may activate TGF_β from its latent to its active form. TGF_β is a mitogen for osteoblasts, and it is one of the very few cytokines that will induce osteoblasts and other connective tissue cells to make extra matrix. So this may be a mechanism whereby resorption is linked to new bone formation.

Osteoblasts have turned out to be even more dramatic than many other cell types in the repertoire of cytokines and growth factors they produce. The list of factors that osteoblasts are known to make includes interleukin-1, tumor necrosis factor, interleukin-6, colony-stimulating factors, fibroblast growth factor, platelet-derived growth factor, parathyroid-hormone-related peptides; there are probably many others. So within bone it may not always be necessary for the other cells that are the traditional producers of these factors to be present, because under appropriate conditions the osteoblasts themselves can produce these factors. This may also be important in the crosstalk between osteoblastic and osteoclastic activity within bone.

A few further examples from other disease states may be of interest in this discussion. First of all, there is the production of interleukin-6, which is the acute-phase mediator, from bone. For example, in osteomyelitis or rheumatoid arthritis, the reason for changes in ESR and so on is not necessarily because there are effects on macrophages and monocytes, but because the connective tissue cells themselves produce the interleukin-6 mediator that then goes off to act on the liver. One of the best inducers of interleukin-6 from bone is in fact interleukin-1. So this could easily happen during any sort of acute inflammatory process in the region of connective tissues.

Clinical Outcome: Antibodies against Interleukin-6 Inducing Remission of Myeloma? One particularly dramatic example is the interplay between myeloma and bone. Myeloma cells thrive in bone. One of the mediators of the resorption they cause is probably TNF_β, or lymphotoxin. Interestingly, when TNF_β works on osteoblasts it stimulates the production of interleukin-6 and granulocyte macrophage colony-stimulating factor. Both of these are known to be potent growth factors for myeloma cells. Thus there arises a microenvironment characterized by self-augmenting mutual dependence, in which the myeloma cells stimulate osteoblasts to produce growth factors that allow the myeloma cells to grow. There are reports that the use of antibodies against interleukin-6 has made it possible to obtain remissions in myeloma patients. So these sorts of phenomena may turn out to be very important.

Action of Steroids. When steroids are used in treating patients with, for example, inflammatory arthritis, part of the action of the steroids may be to block the production of certain cytokines. Part of their potency as antiinflammatory agents is probably explained by inhibiting interleukin-1, tumor necrosis factor, and interleukin-6.

The effect of steroids extends into another area, namely osteoporosis. Estrogen is the way to prevent bone loss in postmenopausal women. The action of estrogen on bone has been a subject of controversy for a long time. Putting together all the evidence that has come through in the last two or three years suggests that the way estrogen acts within bone is through growth factors. Estrogen stimulates the production of insulin-like growth factor or somatomedin C from osteoblasts, where it is an autocrine growth factor. It also stimulates the production of TGF_β, which suppresses resorption and augments bone formation. Estrogen also switches off production of bone-resorbing cytokines (interleukin-1 and TNF) from monocytes. So there are multiple ways in which estrogens, acting within bone, will tend to have an anabolic effect on bone mass, which is what is seen clinically.

Mechanism of Action of Cyclosporine: Effects Outside T Cells? Finally, some comments on the mechanism of action of cyclosporine (Fig. 1) that may perhaps be of interest.

The traditional view of cyclosporine actions is that it acts on T cells to switch off the production of a range of cytokines, interleukin-2 in particular, but others as well (Figs. 2, 3). Although cyclosporine's mechanism of action is far from clarified, there is strong evidence that it must work through an intracellular binding protein or group of proteins that have been termed the cyclophilins, which appear to be present in all cells, not just in T cells. These proteins bind with high affinity down in the nanomolar range.

Recent evidence suggests that the cyclophilin protein is in fact an enzyme, which acts as an isomerase for proline residues in proteins. By altering the *cis-trans* configuration of proline residues, it can alter the way protein chains fold. The suggestion is that what cyclosporine does in some subtle way is to bind to this binding protein, interfere with its enzyme activity, and in turn interfere with the folding of intracellular proteins, which may be, for example, transcription regulators, and thereby alter the activity of the binding protein at a genomic level.

But the question still remains, if that is the case, why are cyclosporine effects restricted to T cells? Maybe there are certain types of cyclophilins present in T cells not present in other cells. That's one possibility. Perhaps the targets for the cyclophilin action are T-cell-restricted.

Exploring carefully whether cyclosporine has effects outside T cells reveals some evidence which may be of great interest in relation to rheumatologic disorders, or to psoriasis, or to some other conditions for which cyclosporine is being used. We have found that interleukin-1 stimulation of bone resorption in vitro can be dramatically blocked by cyclosporine in the right concentration range to account for its binding to cyclophilin. So we obtain a 50% maximum effect around the 10^{-8} molar level. The way in which that works is not completely clear, nor is whether it is an effect that requires T cells (which are probably not numerous in these bone resorbing systems). This has led to the idea that maybe there are some effects of cyclosporine that affect cytokines outside T cells, or other cell types.

To summarize: cyclosporine may inhibit bone destruction and the destruction of other tissues

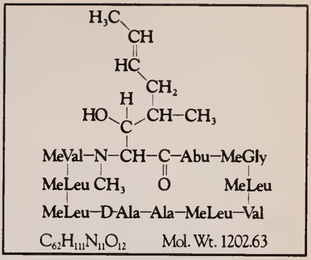
H3C
CH
HC
CH2
H
HO
C
CH–CH3
MeVal–N–CH–C–Abu–MeGly
MeLeu CH3 O MeLeu
MeLeu–D-Ala–Ala–MeLeu–Val
C62H111N11O12 Mol. Wt. 1202.63

Fig. 1. Structure of cyclosporine.

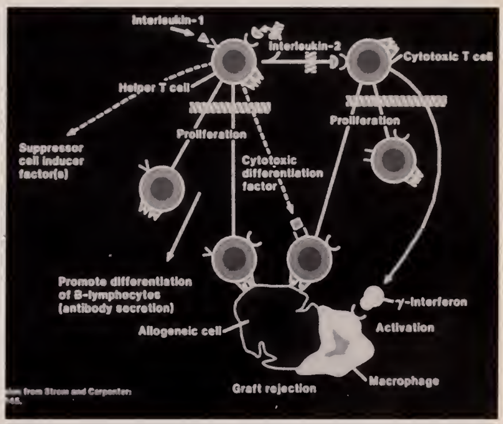
Interleukin-1
Interleukin-2
Cytotoxic T cell
Helper T cell
Proliferation
Proliferation
Suppressor cell inducer factor(s)
Cytotoxic differentiation factor
Promote differentiation of B-lymphocytes (antibody secretion)
Allogeneic cell
γ-interferon
Activation
Macrophage
Graft rejection

Fig. 2. Traditional view of mechanism of action of cyclosporine. Adapted with permission from Strom and Carpenter. Hosp Pract 1983; 18:145.

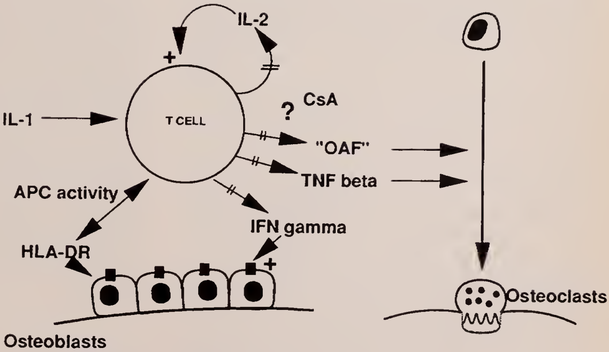
IL-2
+
IL-1
T CELL
?
CsA
"OAF"
TNF beta
APC activity
IFN gamma
HLA-DR
+
Osteoblasts
Osteoclasts

Fig. 3. Possible action of cyclosporine (CsA) in bone, and by extension in gut. T cells produce their cytokines (interleukin-1, IL1; interleukin-2, IL-2; osteoblast activating factor, OAF; tumor necrosis factor, TNF; γ interferon, IFN gamma; antigen presenting cell, APC), some known to be inhibited by cyclosporine. The possibility is that osteoblast interaction with T cells involves class II antigens and γ-interferon coming from T cells to augment crosstalk in terms of antigen presentation, which may be important in disease states. The question whether cyclosporine works only at this level or also has actions within or on osteoblasts or other cell types is open.

induced by several cytokines, particularly interleukin-1. It may be that the responses to cyclosporine that, for example, ameliorate rheumatoid arthritis involve intervention between T cells and either bone cells or chondrocytes, or synovial cells (Fig. 3).

I think this is going to turn out to be a very interesting area. Certainly, looking at the range of effects of cyclosporine in many disease processes discussed by Carstens, Lichtiger, and Appel, it is worthwhile bearing in mind whether they are T-cell-driven events or whether other mechanisms are possible.

References for Further Reading

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Referring again to the title of this symposium, we are talking about scientific basis and about clinical experience. To look at the clinical experience with cyclosporine not just in gastrointestinal disease but also in the broad range of rheumatic and other arthritis diseases to which Professor Russell has raised our consciousness, we turn to Dr. John Carstens. In his position with Sandoz Research Institute, Dr. Carstens really stands at the summit, looking at all the clinical experience with cyclosporine worldwide. In consideration of his unique vantage point on this vast clinical experience, we can forgive Dr. Carstens for being a surgeon.—DBS

Worldwide Experience with Sandimmune (Cyclosporine) in Autoimmune Diseases:

Multiple Sclerosis, Rheumatoid Arthritis, Psoriasis

John Carstens, M.D.

Sandoz has tried to study Sandimmune (cyclosporine) in many diseases. In fact, at one time in the United States we were working on over 40 diseases. We realized, however, that we were failing to make progress on account of our lack of focus. We have therefore concentrated our current efforts outside of the transplantation field on four principal autoimmune diseases: multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

At present Sandimmune has been marketed in the United States for 8 years and in other countries for nearly 10 years. Over 100,000 patients are receiving the drug as treatment for transplantation alone—a good clinical base from which to draw conclusions, at least in regard to transplantation. By contrast, the number of patients with autoimmune diseases treated with the drug is now about 6,000 worldwide. Thus at this point the data on Sandimmune are not as well defined in respect to autoimmune therapy as in respect to transplantation therapy. Sandoz has finished two major, pivotal studies on Sandimmune therapy for multiple sclerosis, for instance, so that we know fairly well what the drug can accomplish in that disorder. For rheumatoid arthritis, the phase II studies are complete, and Sandoz will go on to the pivotal studies. Sandoz's psoriasis studies are in a much earlier phase, as are the studies on inflammatory bowel disease therapy. So the information I am giving here on therapy for autoimmune conditions can only be partial.

The other problems in appraising Sandimmune as therapy for autoimmune diseases resemble the well-recognized problems in assessing clinical activity in Crohn's disease. Which scales can measure drug effectiveness? How can they be used? Are they really valid? In addition, efficacy rates of Sandimmune are different in each of the four autoimmune conditions Sandoz is studying. Dose efficacy is different; toxicity rates differ as well.

This background, I hope, makes plain where the holes in the available data are.

In any event, our story begins in a beautiful but isolated corner of Norway, where a Sandoz employee found and turned over to the Basel office a soil sample that turned out to contain the fungus from which cyclosporine comes.

Cyclosporine is a metabolite of this fungus. It contains 11 amino acids in sequences with aggregate molecular weight 1203 (see Fig. 1 in article by R. G. G. Russell). Sandoz has a parenteral preparation and an oral solution, and will shortly introduce a soft gelatin capsule.

Its actions are quite interesting. Sandimmune has been shown to have the immunosuppressant actions discussed in several articles in this symposium. It has neuroendocrine actions. It has actions on the prostaglandin metabolism. It

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has antiinflammatory actions. It also has antifungal and antiparasitic actions.

Since its mechanisms are thoroughly discussed in Russell's article, I reiterate here only that cyclosporine is a special T-cell modulator that probably works through the cytokine systems.

Pharmacology. Cyclosporine poses a problem of bioavailability; it is a large molecule whose absorption is difficult to achieve. In fact, there are intrapatient differences. Maximum plasma concentrations of cyclosporine are usually reached in 3 to 4 hours. It is transported by a protein or a lipoprotein transport mechanism. Metabolism is at the level of the liver and excretion is primarily fecal, the terminal half-lives being 14 to 27 hours. The most important pharmacologic property of Sandimmune as an immunosuppressive agent is of course its specificity for the helper T cell.

Side Effects. Physicians who prescribe Sandimmune are aware of the gamut of its adverse reactions. Probably the most prominent are excessive hair growth and hyperplasia of the gums.

The side effect of Sandimmune most frequently talked about and most often worried about, however, is nephrotoxicity. Much of the early work on nephrotoxicity was performed in connection with transplantation; the initial dose we were using was 15 to 17 mg/kg. Today we would not recommend such a high dose, not even to treat transplantation patients.

Another major problem can be hepatotoxicity in transplant patients: 4% to 7% of those treated will have hepatotoxicity, manifested by transaminase elevations and especially by bilirubin elevations. These abnormalities are reversible; when the dose is reduced or the drug is withdrawn, transaminase levels usually return to normal.

The other major problem, as in other immunosuppressives, is infections, and they surely exist. In the transplant arena, cytomegalovirus (CMV) is a major problem. As for malignancy: lymphomas do occur, but are quite rare. Among the 100,000 transplant patients treated with Sandimmune, the incidence is now 0.3%. The incidence rate of lymphoma that we now have for the 6,000 patients with autoimmune conditions treated with Sandimmune is about equivalent, 0.4%. There are some differences, however, depending on the underlying disease; one should bear in mind, for example, that the baseline incidence of lymphoma in rheumatoid arthritis patients is higher that it is in other general populations. So it is hard to sort out treatment effects from underlying risks. Nonetheless, in these days of triple-immunosuppressive therapy, malignancy remains a key concern.

Multiple Sclerosis

To provide a sense, albeit incomplete, for the data that Sandoz is developing, I will start by describing two of our studies of approximately 560 patients with multiple sclerosis (MS). They are both double-blind, randomized, placebo-controlled, parallel-group, two-year studies. The study patients have chronically progressive multiple sclerosis, are male and female, and range in age from 18 to 55 years.

Efficacy. As already observed, it is often difficult to assess the efficacy of treatment in patients who have chronic progressive autoimmune diseases. For MS, we used an expanded disability status scale (EDSS), which in many senses is the equivalent of the gastroenterologist's Crohn's disease activity index (CDAI). Like the CDAI, the EDSS has its strengths and its weaknesses, but it is in any event well accepted in the MS field. We also used an incapacity scale (ISS) and other standard scales used in assessment of neurologic disease.

We decided that to "win," that is, to qualify as a treatment success, would require a significant difference in the patient's EDSS or one of the other standard scales.

Of course, it would be much easier just to be able to look at CT scans and say, "Gee, we've cured that patient." But even when patients look much better after treatment, they may still show a lot of plaque on CT scan, so we cannot prove efficacy to the FDA simply from CT scans, or by saying, "Trust me, the patients look better." We need all these clinical assessment scales, arbitrary or flawed as they may be.

In any case, our two pivotal MS studies are examples of how treatment efficacy might be measured by using p values to compare scores on the clinical scales. One study shows clear efficacy with significant p values starting at 9 months and at every three-month interval thereafter (9, 12, 15, 18, 21, and 24 months). The companion study shows efficacy at the end of the treatment period and at several points along the way, albeit not at every point. Perhaps this inconsistency reflects the insensitivity of some of these scales. Nonetheless, the two studies together do show efficacy.

Toxicity. Nephrotoxicity is worrisome, even though we try to soften the anxiety now by calling it renal dysfunction. The mean creatinine levels of the treatment group monitored over 24 months show a fairly significant increase, from 1 to almost 1.4 mg%. However, the mean creatinine values plateau around 4 months and remain steady at that level with no progressive rise, which I believe is a good sign. In fact, when people drop out of the study for one reason or another and stop taking Sandimmune, their mean creatinine values drop almost to baseline within the next 6 months. So for at least the first two years, we can show that the increase in creatinine levels is reversible. BUN levels, as expected, parallel the creatinine value.

Hypertension is another common concern. The mean diastolic pressure in the Sandimmune-treated group is slightly higher, to be sure, but it is not in the range where one would even consider treatment. Still, hypertension is an issue that we continue to watch closely in the Sandimmune treatment of autoimmune disease.

To put the side effect problem into prospective, let us look at the dropout rate from the 560 patients in our two MS studies, probably the largest MS studies ever done. There were 31 dropouts in the cyclosporine-treated group over 2 years, and 1 in the placebo-treated group. Eight (3%) of the Sandimmune-treated patients dropped out for hypertension, defined as any blood pressure with a diastolic higher than 90 mm Hg. Another 13 patients (5%) had renal dysfunction, defined as a sustained >50% increase in creatinine over baseline value, which necessitated dropping the patient or reducing the dose.

Overall, then, what we see here is a toxicity rate that is relatively quite low as the price for an effective treatment for chronic progressive MS. Sandoz is therefore going to be submitting a New Drug Application for Sandimmune in MS, since we feel that the risk-benefit ratio in that disease is quite advantageous.

Rheumatoid Arthritis

On rheumatoid arthritis, the best study is a Canadian multicenter study in which there were 144 patients, 72 taking Sandimmune. The other studies are smaller pilot studies that we did to get a feel for the drug in this patient population. The rheumatoid arthritis patient population is different from that with MS because their kidneys have already been affected by long-term exposure to nonsteroidal antiinflammatory drugs (NSAIDs) and are therefore much more sensitive to Sandimmune. We have been trying to work out the problems of interaction between Sandimmune and NSAIDs; we have not yet completed this analysis, but it is an issue of great concern.

What we can say at this point, though, is that from our earlier studies with rheumatoid arthritis we have gained experiences with what we today would consider a high dose of Sandimmune, beginning at 6 mg/kg per day and even as high as 8 mg/kg per day. Subsequent studies employed lower doses, for example, one at 2.5 mg/kg per day; in the most recent large Canadian study, the dose started at 2.5 mg/kg per day and ended with a mean dose of 3.7 mg/kg per day. These levels compare to mean doses of 5.0 to 5.4 mg/kg per day in the earlier studies. This experience enables us to show the different incidences of side effects such as renal dysfunction and hypertension at different doses of cyclosporine. Although similar efficacy was achieved by both the high and the low doses, even as early as two months, there were big differences in toxicity.

For example, in both the high-dose and low-dose studies, the response rates were striking, ranging from 77% to 93% of the patients demonstrating improvement in joint counts of between 70% and 100%, with corresponding improvements in swelling counts and in global assessments by both patient and physician. It is noteworthy that many or most of the patients who responded so well to Sandimmune had already failed to respond to methotrexate.

The combined experience from our high-dose and low-dose studies showed that we could detect response rates of about 40% even with Sandimmune doses as low as 1.25 to 2.5 mg/kg per day, and that we had already achieved maximal response rates in the range of 4 mg/kg per day. But doses of 6 to 8 mg/kg per day for the rheumatoid arthritis patients brought dramatic evidence of renal dysfunction, with 80% increases in creatinine values. Other studies with relatively high doses also showed creatinine increases of 35%–40%. Although the creatinine levels did plateau and eventually came down with dose reduction or discontinuation of the cyclosporine, it was still somewhat worrisome that the higher creatinine levels took longer to come down and did not always return all the way to baseline. At these high doses, there were also corresponding changes in both inulin and PAH clearance.

Our recent large Canadian multicenter study, by contrast, was conducted at lower Sandimmune doses and it showed much less impact on renal function. There was only a 26% increase in creatinine, and the levels returned completely to baseline within a few months of drug withdrawal. So we can see that even in rheumatoid arthritis patients with prior kidney exposure to NSAIDs, we can achieve maximal therapeutic effects with relatively low doses of Sandimmune that produce little in the way of nephrotoxicity.

The conclusions are similar with regard to hypertension. In the high-dose studies, 40%–50% of patients needed new treatment for hypertension, as opposed to only 8%–10% in the low-dose studies. All this experience in rheumatoid arthritis shows the sharp differences in side effects between high and low doses of Sandimmune in a population with very sensitive kidneys.

Psoriasis

The third principal area of autoimmune disease that Sandoz is currently investigating is psoriasis. Although our data are still limited, we are finding good improvement in patients treated at a low dose of 3 mg/kg.

Conclusion

The bottom-line message from all our experience to date with Sandimmune in autoimmune disease—specifically multiple sclerosis, rheumatoid arthritis, and psoriasis—is that we can achieve significant therapeutic benefit, even in resistant patients, at doses low enough to avoid widespread hypertension or severe nephrotoxicity, even in patients with vulnerable kidneys.

Now we apply the cyclosporine experience specifically to inflammatory bowel disease, starting with an open-label experience that has been a gleam in the investigator's eye for many years. Dr. Simon Lichtiger, when he was still a fellow in gastroenterology at Mount Sinai, became intrigued with the potential for the efficacy of cyclosporine in inflammatory bowel disease and proved very tenacious in this interest. In fact, he has been tenacious to the point that now, as a member of the attending faculty of Mount Sinai, he has accumulated, together with Daniel Present, one of the world's largest experiences with the use of cyclosporine in inflammatory bowel disease.—DBS

Cyclosporine Therapy in Inflammatory Bowel Disease:

Open-Label Experience

SIMON LICHTIGER, M.D.

ALTHOUGH the etiology of inflammatory bowel disease is unknown, immunologic mechanisms are thought to play a pivotal role. Immunosuppressive drugs such as steroids and 6-mercaptopurine (6-MP), as well as other agents with immune-suppressing qualities, including sulfasalazine and metronidazole, have proven to be effective in the treatment of inflammatory bowel diseases. However, there has been a dearth of newly developed therapeutic agents for these disorders. Since the original Truelove and Witts paper describing corticosteroid treatment in 1955, no other agent has been shown to induce rapid remissions in both Crohn's disease and ulcerative colitis. Methotrexate, which was studied by Kozarek's group in Seattle, has already proven to be efficacious in refractory inflammatory bowel disease, but it has not yet been subjected to a placebo-controlled trial. Variations of sulfasalazine—both oral and topical—have been shown to be effective in the treatment of colitis, and preliminary data have suggested promise for the use of chloroquine and hydroxychloroquine in the treatment of inflammatory bowel disease. However, all these drugs act relatively slowly, thereby leaving steroids as the sole bastion of treatment for severe flareups of inflammatory bowel disease.

Background

Cyclosporine, a targeted and rapidly effective immunosuppressant, has revolutionized the transplant field. By effectively blocking the replication of messenger RNA, it seems to interfere with the inflammatory cascade. Its usefulness has been proven in organ transplantation and in several autoimmune disorders. Behçet's disease, pyoderma gangrenosum, and uveitis, all related in some way to inflammatory bowel disease, have been reported to respond to cyclosporine therapy.

Recently, the literature on cyclosporine treatment for inflammatory bowel disease has expanded. Initially, the uncontrolled data on Crohn's disease, most of which came out of Europe, showed anecdotal success in 60%–70% of patients. The much-awaited controlled study from Brynskov's group in Denmark showed effectiveness in 59% of studied patients with moderate Crohn's disease. In ulcerative colitis, the experience is a little bit more limited. I think that is because ulcerative colitis is, at least in Europe, viewed as much more amenable to surgical treatment than it is in America. Therefore, most of the uncontrolled data are basically our own from Mount Sinai. We also see a response rate of about 60%. In all of the studies, the response to treatment occurred within two to three weeks, and only a modicum of toxicity was noted.

What were some of the problems with all

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these previous studies? In Crohn's disease, many of the criteria for entry were heterogeneous. In other words, Crohn's disease is not like ulcerative colitis, where the clinical manifestations are basically the same from one patient to another. Patients with Crohn's disease may have fistulous, obstructive, or simply inflammatory disease, and in the Danish double-blind study, patients were not stratified on the basis of their manifestations, or with respect to prior therapy. In other words, these disparate groups of patients were lumped together in a single study, whereas they probably should have been stratified into subcategories.

There was also a question of malabsorption of the oral cyclosporine. Patients with Crohn's disease often have involvement of the small bowel, which is the site of absorption of cyclosporine. The shorter the extent of normal small bowel, the lower the cyclosporine level, and I believe there is a correlation between subtherapeutic levels and lack of response. These factors prompted us to use parenteral cyclosporine initially, followed by a prolonged phase of oral treatment.

Atkinson noted that there were subtherapeutic levels due to erratic absorption in transplant patients with radiation enteritis, diarrhea, anemia, or hypoalbuminemia. He also noted that bolus injections of cyclosporine rapidly produced toxic levels followed by a quick fall to subtherapeutic levels, so we decided to administer the cyclosporine by continuous infusion in order to assure steady therapeutic levels with minimal toxicity.

Ulcerative Colitis

In ulcerative colitis, our protocol has two phases. The acute or parenteral phase of treatment lasts for a maximum of fourteen days, followed by long-term or oral treatment, which lasts for six months. It is important to realize that all the patients in our study are terribly ill; they have all met the Truelove and Witts criteria of severity and have failed to respond to steroids, and they are all being prepared for colectomy.

The initial dose of cyclosporine is 4 mg/kg per day by continuous infusion. The goal of the acute phase of treatment is simply to avoid colectomy during hospitalization. This goal is based on the Truelove approach, Järnerot's experience, and Meyers's data, all of which showed that patients with severe ulcerative colitis who fail to respond to parenteral steroid treatment administered for up to ten days require colectomy. The ten-day criterion for lack of therapeutic response means that over 95% of patients will need colectomy.

If patients successfully respond to treatment in this acute phase and make a specified degree of improvement in clinical score based on modified Truelove and Witts criteria, they go on to the long-term treatment phase. During this phase, they receive oral cyclosporine, initially at 5–8 mg/kg per day and thereafter at decreasing doses, with careful monitoring of their renal function and cyclosporine blood levels. The goals of the long-term treatment are withdrawal from steroids, endoscopic healing, and clinical remission.

We have recently been entering into our ulcerative colitis study patients who have chronic disease refractory to conventional therapy, including 6-MP, and who have either had steroid toxicity or are steroid-dependent, defined as requiring more than 20 mg/day of prednisone for three months. With respect to exclusion criteria, we can afford to be very strict because we are dealing with a population different from transplant patients. Most of our ulcerative colitis patients are young adults who are healthy except for their bowel disease. Very few of them have had long-term nonsteroidal treatment and very few have any renal dysfunction. Therefore, we exclude anyone with a BUN level over 22, a creatinine level over 1.2, or a creatinine clearance less than 90 cc/min, as well as anyone who is hypertensive (defined as greater than a systolic pressure of 150 mm Hg or a diastolic pressure of 90 mm Hg), or who has received any investigational drug within the last three months.

Clinical scores are tabulated on day one and on day seven. The scores are based on clinical signs and symptoms: abdominal pain, diarrhea, fecal incontinence, amount of blood in stool, use of antidiarrheals, degree of abdominal tenderness on physical examination, subjective general well-being, and the physician's global impression of the patient's quality of life.

If the patients have improved sufficiently by day seven, they are then transferred to oral treatment, which continues for six months. If the patients are only moderately better by day seven, parenteral therapy is extended to fourteen days, when clinical assessment is performed again. Patients are classed as failing to respond to the acute phase if there is clinical deterioration or if their clinical score does not improve by at least 50%; the attending surgeon also has the prerogative of declaring failure of medical therapy at any point. In these cases, we advise immediate colectomy and terminate the study.

Those patients who achieve sufficient im-

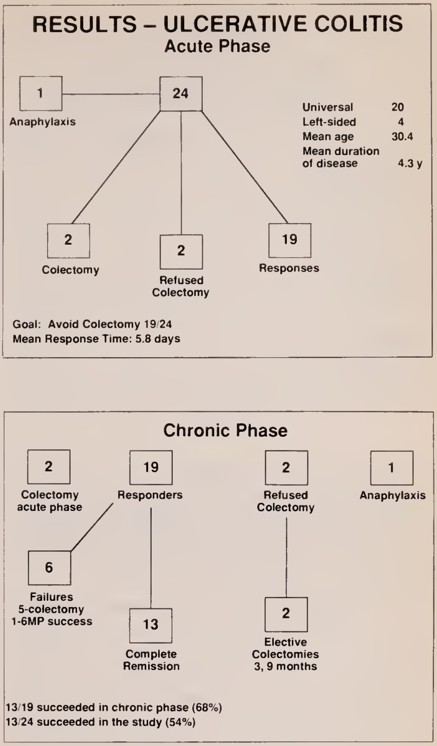
RESULTS – ULCERATIVE COLITIS
Acute Phase
1
Anaphylaxis
24
Universal 20
Left-sided 4
Mean age 30.4
Mean duration of disease 4.3 y
2
Colectomy
2
Refused Colectomy
19
Responses
Goal: Avoid Colectomy 19/24
Mean Response Time: 5.8 days
Chronic Phase
2
Colectomy acute phase
19
Responders
2
Refused Colectomy
1
Anaphylaxis
6
Failures
5-colectomy
1-6MP success
13
Complete Remission
2
Elective Colectomies
3, 9 months
13/19 succeeded in chronic phase (68%)
13/24 succeeded in the study (54%)

Fig. 1.

provement to avoid colectomy and leave the hospital then enter the long-term phase of the study and are followed up while taking oral cyclosporine and decreasing dose of steroids. In this phase the introduction of new medications, including sulfasalazine or its analogs, is not allowed. Patients are allowed, however, to continue previously established sulfasalazine treatment and resume topical enema therapy if they were on it prior to the flareup. Serum BUN and creatinine levels and 24-hour urine collections for creatinine clearance are obtained at approximately one-week intervals.

Final scoring is carried out after the patient has completed the six-month trial, and success is defined as both clinical remission and endoscopic healing. To date, among 24 patients with ulcerative colitis who have completed the entire study (Fig. 1), 20 had universal colitis and 4 had left-sided disease. Their age range was from 12 to 52 years, and mean duration of disease was 4.3 years. Among these 24 patients, 2 underwent colectomy in the hospital phase, 2 failed to respond to intravenous cyclosporine but refused colectomy at that time, and one had an anaphylactic reaction to the cremaphor, which is the carrier in the intravenous form of cyclosporine. All 5 of these patients are considered failures of treatment. The other 19 responded, making an 80% response rate in this acute phase of the study.

Of these 19 acute-phase responders, 13 (68%) have gone on to complete the long-term phase of the study successfully. The other 6 patients comprise 5 who have undergone colectomy and one who chose instead to continue medical treatment with 6-MP and is currently well. Overall, therefore, 13 of the original 24 patients who were enrolled in the study (54%) have successfully completed both the acute and chronic phases of the study and are doing well at the present time.

All of these patients, of course, had been considered medical failures and candidates for colec-

TOXICITY

Adverse Effects of CSA in the Treatment of IBD (n=41)

	Mild	Moderate	Severe
Nephrotoxicity	2	1	0
Hepatotoxicity	0	0	0
Parasthesias	16	1	1
Hypertension	8	0	0
Headache	1	1	0
Infection	0	0	0
Tumor	0	0	0
Anaphylaxis	0	0	1

Fig. 2.

tomy at the time of initiation of cyclosporine therapy. The therapeutic response rate did not vary with blood levels of cyclosporine so long as the levels were anywhere within the therapeutic range, but a subtherapeutic level was clearly a harbinger of subsequent clinical flareup.

On completion of the study, these 13 patients have been followed up for 8–24 months, off cyclosporine and on maintenance therapy, either sulfasalazine alone or sulfasalazine plus 6-MP. Twelve of the 13 have remained in sustained remission; one patient had a clinical flareup after one year off cyclosporine and responded without problems to a course of intravenous ACTH.

Crohn's Disease

Crohn's disease is even more difficult to treat than ulcerative colitis. We have studied 17 patients with intractable Crohn's disease who had failed to respond to various medical therapies, including immunosuppressants. They had enterocutaneous or perirectal fistulas, as well as severe extraintestinal manifestations. As in the Crohn's disease trial of 6-MP by Present, Korelitz, et al, we set therapeutic goals for each patient depending upon his or her principal clinical problem. Ten patients were treated chiefly for fistulous disease (7 perirectal, one rectovaginal, and 2 enterocutaneous); 6 were treated mainly for steroid-sparing effect, and one for severe pyoderma gangrenosum. Most of the patients were also chronically beset by pain, diarrhea, and what we recorded as poor quality of life. As with our ulcerative colitis study, all patients were first entered into a limited parenteral treatment phase, followed by a prolonged oral cyclosporine treatment phase. These patients have now been taking cyclosporine for prolonged periods, with a mean duration of 10.4 months and a range up to three years. The mean oral dose at the six-month point has been 4.8 mg/kg per day. These long treatment intervals reflect the difference in treating Crohn's disease, which never fully heals but is pushed into remission, as opposed to ulcerative colitis, in which mucosal healing seems to allow maintenance of remission with other medications. Indeed, several patients have simply refused to discontinue their cyclosporine.

Of the ten patients who were treated primarily for refractory fistulous disease, six have had moderate to excellent responses, the latter defined as complete closure of the fistulas; others have had at least mild responses.

Very little toxicity has occurred (Fig. 2), perhaps because we are dealing with a population of patients who have normal baseline cardiovascular and renal function. Of the total of 41 patients in our combined ulcerative colitis (24 patients) and Crohn's disease (17 patients) series, two patients have had mild nephrotoxicity (33% increase in serum creatinine or 33% drop in creatinine clearance), which reverted to normal on decrease of dosage of cyclosporine, and one patient has had moderate nephrotoxicity (50% increase in serum creatinine), which did not respond to decreasing the dose and required stopping the medication. It is noteworthy that this last patient, on stopping the cyclosporine, experienced a severe flareup of his underlying pyoderma gangrenosum and had to be transferred to the University of Pittsburgh for further immunosuppressive treatment. We have observed no hepatotoxicity and no severe neurotoxicity, which is a problem chiefly in patients who are hypomagnesemic or hypocholesterolemic.

On the other hand, we have seen a fair degree of minor neurotoxicity, including lower extremity paresthesias, similar to those experienced with metronidazole. One patient with ulcerative colitis had an anaphylactic reaction to the intravenous cremaphor, which is the carrier for the intravenous cyclosporine. The reaction was characterized by wheezing and flushes, and was responsive to subcutaneously administered epinephrine. No opportunistic infections have been observed, and of course our experience to date has been too short to comment on the risk of neoplasia, which has been reported as 1.3% in long-term treatment in the transplant population, who seem to carry an inherently greater risk of carcinoma anyhow.

Conclusions

Intravenous cyclosporine is rapidly effective in the treatment of severe ulcerative colitis. Colectomy was avoided in 19 of 24 patients (80%) in the acute phase of our study. In the chronic phase, oral cyclosporine maintained remissions in 13 of the 19 patients (68%), for an overall response rate of 13 of 24 patients (54%). Cyclosporine is steroid-sparing in ulcerative colitis, as all of the patients who were considered successes were maintained on less than 5 mg of prednisone daily. The rationale for maintenance of a small dose of steroids is based on a possible synergistic effect of low-dose prednisone and low-dose cyclosporine in blocking both interleukin-1 and interleukin-2. Follow-up has been up to two years post-study, and only one of the 13 has had another clinical flareup, which was responsive to intravenous ACTH. We have not seen any long-term complications in this group, and one episode of moderate nephrotoxicity was reversed on decreasing the dose of cyclosporine.

In Crohn's disease, cyclosporine may be particularly effective in the treatment of fistulas. Six of our ten patients (60%) had moderate to complete improvement in perirectal, rectovaginal, or enterocutaneous fistulas. These data are corroborated by a recent report (1). Cyclosporine is also steroid-sparing in Crohn's disease; our patients decreased their mean daily prednisone dose from 36 mg to 12.5 mg. Patients with diffuse small-bowel disease may malabsorb oral cyclosporine, however, so that careful monitoring of blood levels is necessary to maintain a therapeutic range.

Encouraged by our good therapeutic results, with so little toxicity, we are now initiating a randomized, double-blind, placebo-controlled study of cyclosporine, both in ulcerative colitis and in Crohn's disease, in cooperation with the University of Chicago and UCLA. The future of inflammatory bowel disease therapy thus seems to hold great hope and promise.

References

1. Strange EF, Flieg WE, Rehklau E, Ditchuneit H. Cyclosporine A treatment in inflammatory bowel disease. Dig Dis Sci 1989; 34:1387–1392.

We cannot talk about cyclosporine without talking about the kidney, and no one is better equipped to deal with these two topics, and to draw their lessons for the gastroenterologist, than Dr. Gerald Appel. Fortunately for the readers of this symposium, Dr. Appel combines two special talents: he has vast clinical experience with the renal effects of cyclosporine, and he is a repeated winner of awards for excellence and distinction in clinical teaching.—DBS

Cyclosporine and the Kidney:

Lessons for the Gastroenterologist

GERALD APPEL, M.D.

THE USE of cyclosporine to treat inflammatory bowel disease is discussed well and widely elsewhere in this issue. Better decisions on who will benefit from use of the drug can be made when the physician knows more about cyclosporine itself. As the only nephrologist in this gathering of experts, I bring some lessons for gastroenterologists and other clinicians from nephrologists, who have been using cyclosporine since 1983 to treat transplantation patients. Some now use it to treat the nephrotic syndrome, systemic lupus, and other diseases that have similarities to inflammatory bowel disease. First I take up drug administration, drug levels, and drug interactions—very important issues. I then discuss the issue of nephrotoxicity, and the syndromes of renal dysfunction, their significance, and how to avoid them. A most important question for the clinician is, "Are these syndromes of dysfunction significant in the treatment of my patients or are they not?" I talk about other side effects, some mentioned in other articles. Finally, I talk about cyclosporine therapy in nontransplantation renal diseases, because these are most similar to the treatment situation in inflammatory bowel disease.

Administration and Pharmacokinetics

The administration of cyclosporine and its pharmacokinetics raise some important considerations. Until recently only an oral solution was available for patient's self-administration, making it a difficult drug for patients to use. Patients must pour the liquid suspension into a real glass (it cannot be used in a styrofoam cup), and it has to be taken with certain liquids: chocolate milk, milk, apple juice, for example. Patients have to be carefully instructed in the use of cyclosporine; if they are not, absorption will be very erratic. Oral capsules have recently become available and appear to be equivalent to the liquid suspension in bioavailability.

Second, an intravenous preparation is available. In general, the intravenous dose is about one-half to one-third the oral dose. Clearly a major reduction in the dose is needed when it is administered intravenously.

Third, and probably most important: there is tremendous interpatient and intrapatient variability in absorption of this drug. If two different patients are given the same dose, even though they have the same body weight and the same habitus, tremendous differences in their drug levels and in therapeutic efficacy may be found. Likewise, a patient who is stable on the drug may several months later suddenly have a significant rise or decrease in the level of the drug, although the dose has not changed.

The drug binds to plasma lipoproteins and red cells. Blood levels are at least twice as high as serum levels because of the binding to red cells. Cyclosporine is metabolized by the liver by the cytochrome P450 system. This is very important

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Adapted from the author's presentation at the seminar "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" held at The Mount Sinai School of Medicine, December 8, 1989. From the Department of Clinical Nephrology, Columbia-Presbyterian Medical Center. Address reprint requests to the author, who is Director, Clinical Nephrology, and Professor of Clinical Medicine at Columbia Presbyterian Medical Center, 622 West 168th Street, New York, NY 10032.

TABLE

Drugs that Alter Blood or Serum Levels of Cyclosporine

Cause elevations
Diminish metabolism of cyclosporine
- Erythromycin
- Ketoconazole

Increase bioavailability of cyclosporine
- Metoclopramide

Cause decreases
Increased metabolism
- Rifampin
- Dilantin

for drug interactions. Drugs that interfere with this metabolic system can cause tremendous variations in cyclosporine efficacy and toxicity.

There are active metabolites of the drug, and a number of drug interactions are important for all clinicians. Even if the physician's own patients are not taking cyclosporine, you will still see patients of other clinicians including patients with renal diseases, transplantations, uveitis, Graves disease and so on. Cyclosporine is clearly being tried in many disease states and you have to know how to handle the drug.

There are at least three major points on the cyclosporine molecule (see Fig. 1 in article by Russell) where substitutions can occur due to metabolism. Some of these metabolites are active, and have immunosuppressive properties. Others may be related to toxicity. Different metabolites may accumulate in different situations, and different assays measure the parent compound with or without the metabolites as well. Again, cyclosporine is not a simple medication to use.

Maintaining Drug Use. Cyclosporine levels for transplantation patients have a narrow therapeutic window; the difference between toxic and subtherapeutic levels is relatively narrow. There is significant variability in cyclosporine levels between patients and within patients themselves over time.

What is a toxic level of the drug? What a nephrologist at Columbia Presbyterian considers toxic for a patient with a renal transplant would not necessarily be the same as what a cardiologist at Presbyterian Hospital considers toxic for a patient with a heart transplant. For a patient with a nephrotic syndrome I might aim at still a third level. Patients develop toxic symptoms at different levels, and different diseases have different therapeutic responses. What is subtherapeutic for renal transplantation is not necessarily so for a patient with idiopathic nephrotic syndrome. Some of the nephrotic patients with very low blood levels will remain in complete remission of nephrotic syndrome. Yet the drug obviously has an effect, because when patients stop taking it completely they rapidly relapse. So very high levels of drug mean high risk of nephrotoxicity; and very low levels of drug probably mean low delivery of drug and no effect. But the range is broad.

What about assays? High-performance liquid chromatography is cumbersome and time-consuming and measures on the parent compound. The radioimmunoassay, which is used extensively, measures the metabolites as well. This is reasonable since some of the metabolites are active. Whole blood levels are usually at least twice the plasma or serum levels. The most important thing to understand about levels of cyclosporine is to understand what your own institution's or laboratory's levels mean. I cannot compare the values at Columbia-Presbyterian with those at other institutions. The clinician has to look at his or her own laboratory's values and say, "This is in the therapeutic range; this is not in the therapeutic range" for the given patient population with a given disease state.

Drug Interactions. There are two major types of drug interactions to be concerned about with cyclosporine: those that elevate and those that decrease drug levels (Table).

First, elevated serum levels can be seen when there is diminished metabolism of cyclosporine. Drugs which interfere with or counteract the effect of the cytochrome P450 system do this. Two such extremely important drugs are erythromycin and ketoconazole. The clinician must reduce and monitor the dose of cyclosporine if erythromycin or ketoconazole is prescribed with the cyclosporine.

For example, a patient on a stable cyclosporine dose who undergoes a course of erythromycin treatment for a streptococcal throat, or a course of ketoconazole, may experience a tremendous rise in levels of cyclosporine, and at the same time a rise in serum creatinine; the level will come down when eythromycin or ketoconazole treatment is ended, and when the clinician lowers the cyclosporine levels.

Metoclopramide, by increasing the bioavailability of cyclosporine, can also cause increased serum levels. The calcium channel blockers diltiazem, verapamil, and nicardipine may also cause major increases in cyclosporine levels.

Increased metabolism by the cytochrome P450 system can cause low cyclosporine levels and a subtherapeutic response. Rifampin, now used for many infectious diseases other than tuberculosis, does this, as do dilantin and virtually all the other anticonvulsants. These agents will markedly decrease levels of cyclosporine, at times reducing efficacy as well.

Nephrotoxicity

There are several patterns of renal dysfunction produced by cyclosporine.

Cyclosporine clearly can produce an acute reversible decrease in the glomerular filtration rate (GFR). If the dose is lowered, the GFR improves and BUN and creatinine levels return to normal. This is extremely common.

In a very small number of patients, cyclosporine can produce microvascular disease, which looks like the hemolytic uremic syndrome or TTP. This is very rare.

Many patients who have acute tubular necrosis (ATN) after transplantation and are taking cyclosporine have a much more prolonged period of oliguric acute renal failure than patients with ATN not taking cyclosporine.

The most important dysfunction is chronic irreversible renal damage with interstitial fibrosis and scarring of the kidney.

Originally most nephrologists felt that cyclosporine was a glomerular toxin causing glomerular sclerosis, or a tubular toxin causing ATN and tubular damage. Now many nephrologists and most people working in the field feel major changes are related to functional and structural vascular changes. It is predominantly the vasculature of the kidney that is involved.

Acute Nephrotoxicity. In animal models the acute reversible decrease in glomerular filtration rate is due to vasoconstriction. It is associated with an increase in renal vascular resistance. A number of different mechanisms have been proposed to be involved here. There does not appear to be major support for involvement of the renin-angiotensin system or the sympathetic nervous system. However, recent studies suggest that cyclosporine in vivo and in vitro releases endothelin from epithelial cells. Endothelin is the most potent vasoconstrictor known. If in animals the effect of endothelin release is blocked with endothelin antibodies, cyclosporine produces no vasoconstriction. So this may be both a mechanism of vasoconstriction and of hypertension as well.

Evidence for altered prostaglandin metabolism comes from Remmuzzi's group in Bergamo, Italy. They have created an animal model of decreased GFR with cyclosporine by giving large doses orally for 7 weeks to rats. The GFR plummets after the 7 weeks of cyclosporine administration. If these animals are given a thromboxane synthetase inhibitor, the glomerular filtration rate markedly improves but does not return to normal. Thus, part of the decrease in GFR may be due to thromboxane synthesis and altered arachidonic acid metabolism. Again, this is reversible.

Prolonged acute renal failure in the ATN setting is also probably due to renal vasoconstriction. This is often reversible by reducing the dose of the drug.

Renal microvascular thrombotic disease, with a TTP-like picture, can be disastrous when it occurs. However, only about 20 cases of this condition related to cyclosporine use have been reported in all of the renal transplant literature. It is extremely uncommon. It may be more common among bone marrow transplant patients. I am unaware of its occurrence in patients who are receiving cyclosporine for other indications. This is felt to be a rare form of toxicity to endothelial cells.

Long-Term Nephrotoxicity. A big question for nephrologists and for all who prescribe cyclosporine for inflammatory bowel disease or any other condition is the question of chronic nephrotoxicity. What should physicians expect in their own patients? Only recently have a few good animal models been developed after long exposure of the animals to cyclosporine.

Several pathologic changes have been shown to occur: a unique form of damage to the arterioles of the kidney (arteriolopathy), tubular atrophy, and interstitial fibrosis, again in a unique pattern of so-called striped fibrosis.

Other important questions are, How progressive is the chronic renal damage, and what is its role in leading to end-stage renal failure? If a patient is treated with cyclosporine, can the patient be expected to end up on dialysis ten years from now? A number of studies from Stanford have looked at heart transplant recipients who have received either cyclosporine or azathioprine along with steroids as the immunosuppressive agent. In these studies, after 12 months the Imuran-treated patients had good renal function, whereas the cyclosporine-treated patients' renal function was not as good. The pathologic changes occurring with cyclosporine use included segmental and global glomerular sclerosis and interstitial scarring.

A major question is, Does this happen to all the patients who get cyclosporine at whatever dose they receive, and does it lead to progressive renal failure? In a recent follow-up study published recently, the Imuran-treated patients at 1, 6, 12, and 24 months had serum creatinine levels of 1, 1.2, 1.2, 1.2 mg/dL respectively. The cyclosporine-treated heart transplant patients at 1, 6, 12, and 24 months had serum creatinine levels of 1.3, 1.9, 2.1, 2 mg/dL respectively. This looks reassuring in that the serum creatinine is not rising with time among cyclosporine-treated patients. Even longer-term data on patients who received cyclosporine after a heart transplant show that the glomerular filtration rate does appear to stay stable for up to 3 to 4 years. However, repeat biopsies on some patients reveal more glomerular sclerosis and some greatly enlarged glomeruli, implying that remaining glomeruli are hyperfiltering and doing more work. Thus, the investigators at Stanford felt there was progressive damage with cyclosporine over time. Other groups dealing with transplantation feel that this is not true.

The classic pathologic changes of chronic cyclosporine nephropathy include marked narrowing of the blood vessels due to the arteriolopathy. Blood vessels are markedly narrowed by insudation of plasma protein and thickening of the wall. Another characteristic change of chronic cyclosporine nephropathy is striped fibrosis; between the patches of normal tubules are broad stripes of fibrous tissue. Glomerulosclerosis is found as well.

Good animal models of cyclosporine nephropathy have only recently been developed. In many of these animal models the blood flow is relatively well maintained. In humans a major decrease in blood flow seems to occur when there is cyclosporine nephrotoxicity. Sorting out the relationship of the arteriolopathy, which may be primary to the entire picture, is difficult.

To assess cyclosporine nephrotoxicity, the sine qua non is a drop in the glomerular filtration rate, usually with a rise in BUN and serum creatinine levels. Often there is associated hypertension and hyperkalemia. A number of drugs may cause a potentiation of cyclosporine nephrotoxicity, including nonsteroidal antiinflammatory drugs, contrast agents, and aminoglycoside antibiotics. Many of these drugs are known nephrotoxins and will potentiate the nephrotoxicity of any agent. For a patient taking cyclosporine, care must be exercised about amphotericin, aminoglycosides, contrast agents, and especially now, agents that inhibit prostaglandin synthesis, aspirin, and the nonsteroidal agents.

Other Side Effects of Cyclosporine Use

Clinicians should be aware of a number of other side effects of cyclosporine.

Hepatotoxicity is extremely rare in the many patients I have seen who are taking cyclosporine to treat transplantation, nephrotic syndrome, lupus.

Neurologic problems are not as rare, but usually consist of tremors that respond to lowering the dose of the drug.

Hypertrichosis and gingival hyperplasia can both be very bothersome to some patients. Telling patients with gingival hyperplasia to brush their teeth more does not help at all, and it just makes their gums bleed more. Flossing sometimes helps, but usually the hyperplasia responds quickly to lowering the dose of the drug; again, this side effect seems to be dose related.

Neoplasms have been reported with cyclosporine use. I have yet to see any neoplasm that I can in any way relate to cyclosporine. Having personally taken care of hundreds of transplant patients at Columbia and elsewhere over many years, I have seen a handful of neoplasms. I can only think of two lymphomas in the entire time period, and both patients were taking Imuran, not cyclosporine. Nevertheless, malignancies are a potential problem with all *long-term* immunosuppression.

Cyclosporine can cause both hypermagnesemia and hypomagnesemia: hypermagnesemia with renal dysfunction, hypomagnesemia due to tubular wasting. Likewise, uric acid may be up or down, but it is usually elevated, and gout is more frequent among cyclosporine-treated patients.

Two major side effects are hypertension and hyperkalemia. Patients taking cyclosporine will have high blood pressure, and some will have elevated serum potassium. Hypertension is relatively frequent in certain populations, especially if the dose of cyclosporine is high. The mechanism, again, is not clear; it may be related to endothelin release and is probably not renin-mediated. (Even though some measured renin levels are high, when the measurements are careful it is the prorenin level that is high, not renin itself. The actual renin levels turn out to be low in patients taking cyclosporine.) In general, the hypertension is usually mild to moderate and is easily treatable. It is something to be aware of, but does not limit use of the drug.

Hyperkalemia is also common in the cyclosporine-treated transplant population. In some groups up to a quarter of the patients have had significant hyperkalemia, and many require treatment for this. The aldosterone and renin levels are usually low or normal, and the bulk of the evidence seems to be that these patients cannot excrete a potassium load. They appear to have tubular resistance to aldosterone and do not transport potassium easily across their renal tubules. The treatment of this hyperkalemia is a low-K+ diet, avoidance of K+ supplements, and absolute avoidance of diuretics that spare K+. Insulin-dependent diabetics are especially prone to hyperkalemia because their levels of renin or aldosterone are so often low and their potassium levels must be monitored carefully if they are to be treated with cyclosporine.

Cyclosporine in Nontransplant Renal Diseases

The use of cyclosporine to treat patients with inflammatory bowel disease is not comparable to the transplant situation. In the transplant setting doses of the drug are higher, there is a life-threatening illness, and the physician may have to keep the transplanted organ functioning, especially if it is a heart or a liver or a lung. Using the drug to treat a patient who has inflammatory bowel disease is very different; I think it is more analogous to treating a patient with idiopathic nephrotic syndrome or systemic lupus.

Patients with a number of renal diseases have been treated with cyclosporine, including many patterns of the nephrotic syndrome: minimal change disease, focal sclerosis, proliferative glomerulonephritis. Literature reports on patients with systemic lupus treated with cyclosporine probably add up to over 150 cases. There is even a controlled trial at the National Institutes of Health using cyclosporine for systemic lupus. By anecdotal reports, a handful of other renal diseases have also been treated with cyclosporine.

Although many early studies were poorly done, some recent ones have been reasonable. A recent trial of cyclosporine use for the nephrotic syndrome by Amir Tajani in the Division of Pediatrics at Downstate looked at 20 young patients with steroid-resistant or steroid-dependent relapsing nephrotic syndrome. All of these children had already failed to respond to treatment with either chlorambucil or cytoxan, so the study population was highly drug resistant. When treated for 8 weeks with cyclosporine at a dose of 7 mg/kg, 14 of 20 patients had complete remission of the nephrotic syndrome. This includes 6 with focal sclerosis, often very hard to treat. Six others had a reduction in proteinuria. There was no significant change in glomerular filtration rate; nobody lost renal function during the study. Forty percent had sustained remission of the nephrotic syndrome at one year. Note that the 7 mg/kg dose is close to the transplant maintenance dose, which is usually about 6 mg/kg, not the starting transplant doses, which may be much higher and associated with more nephrotoxicity.

I personally have a patient who has been off and on cyclosporine for resistant idiopathic nephrotic syndrome now for over 4 years already. This young lady has grown fully, developed, has normal height, and has no stretch marks or stria from steroids. She appears to be cyclosporine-dependent; when she stops taking the drug she only goes a couple of months before relapsing. On the other hand, on a very low dose of cyclosporine (1-½ to 2 mg/kg per day) she sustains her remission, and appears to have stable renal function.

A number of controlled trials of idiopathic nephrotic syndrome in adults are now being conducted. A. Merier may have the most extensive experience with long-term therapy. His cyclosporine-dependent patients (patients whose nephrotic syndrome relapses when they are taken off cyclosporine), did not seem to suffer nephrotoxicity at two years, and many of them are followed up for 36 months. On renal biopsy, typical cyclosporine lesions were seen only in 2 patients. He concludes that the vascular and interstital lesions are probably due more to the progression of the basic disease of focal sclerosing nephrotic syndrome than to cyclosporine toxicity. The remissions did not entail unreasonable hazards, and it is reasonable for the clinician worried about cyclosporine nephrotoxicity in this population to do a renal biopsy at one year to find out if any cyclosporine changes are present. In general, Merier finds no cyclosporine nephrotoxicity and that many of these people are doing well.

A good study of the treatment of systemic lupus with cyclosporine comes from the Necker Hospital; these researchers looked at 12 patients with lupus who had not responded to steroid therapy and were then treated with cyclosporine. With cyclosporine there was a marked decrease in proteinuria, a decrease in activity of the disease, and no major increase in fibrosis on renal biopsy in the majority, although one patient did have an increase in fibrosis. During the cyclosporine treatment plasma creatinine levels were elevated, but decreased after 6 months of treatment. The renal dysfunction was thus reversible when the cyclosporine was stopped. In this study, 6 of 12 patients had some nephrotoxicity, and 6 of 12 had hypertension. However, all of the nephrotoxicity and hypertension occurred in the first 6 lupus patients, who received high-dose cyclosporine therapy (10 mg/kg per day). The subsequent 6 patients, treated with 6 mg/kg per day, had no hypertension and no significant nephrotoxicity.

Another recent study published in *Clinical Nephrology* looked at 26 lupus patients who have now been followed up on cyclosporine and low-dose steroid therapy for two years. The activity of their clinical disease decreased. There was a marked reduction in steroid dose over time. Their mean serum creatinine levels started at 100 μM/L and was even lower at the end of two years of therapy. They also underwent marked decrease in proteinuria and improvement in renal morphology. Clearly, this population has done very well with the lower doses of cyclosporine being used.

Conclusion

First, cyclosporine is not the easiest medication to use, this is clear with the oral preparation, learning about administration, drug interactions, thinking about nephrotoxicity, and measuring serum levels. It is a complex drug. But many of the medications we use are complex, and we learn how to handle them.

Second, nephrotoxicity is a major concern, but it may be totally avoidable if the physician uses low-dose therapy and, especially, limits the duration of therapy. As a treatment for immune bowel disease, the niche that this drug may find may be for short-term induction therapy or for 6-month therapy, not therapy that continues for 3, 4, or 5 years as in organ transplant populations.

Finally, it is clear that this is a remarkably effective immunosuppressive drug which we will all see more of in the future.

Questions and Answers

Sachar: Thank you, Jerry. That remarkably clear, comprehensive, and lively presentation helps us understand how you've won those teaching awards. With the use of cyclosporine in lupus and nephrosis, there must be a lot of young women getting this drug who have become pregnant. Can you just give us a word on what happens?

Appel: Yes, I can. First a comment about immunosuppressive therapy in young women. Of all the medication I use to treat immunologic disease (and a great many of the patients I treat are on some form of immunosuppression, whether prednisone, cyclophosphamide, Imuran, or cyclosporine), the one that scares me the most is high-dose corticosteroid therapy. I have no doubt that high doses for long periods of time have the most side effects and are the most toxic. In the lupus population, which has gone through almost everything, we're using intravenous cytoxan, and I certainly feel this is more benign than the high doses of steroids.

On cyclosporine and pregnancy, the only extensive data I know about are in the transplantation literature. In respect to nephrosis and lupus, most physicians encourage their patients not to get pregnant while they're in the middle of a relapse of nephrotic syndrome or while their lupus is active. Among the Imuran-treated transplant patients, of which there is extensive experience now (there must be 800–900 transplant patients who have gone on to pregnancy), there may be a slight increase in birth defects. If so, it is a very small increase. Many normal pregnancies have occurred among patients taking azathioprine. In regard to cyclosporine, the limited information available on only about 40 or 50 births to transplant patients on cyclosporine does seem to suggest an increased incidence of small-birthweight babies. There may also be an increase in micrognathia (tiny jaws), which is obviously a birth defect. Again, because of the small number of births, the statistics aren't clear yet. At the current time, when I have a patient who wants to get pregnant (usually a transplant patient who is doing well) I try to get them to switch over to azathioprine.

One more comment about serum levels: After renal transplantation, many institutions don't even bother anymore to follow serum cyclosporine levels routinely after the first year. I have patients who received renal transplants elsewhere and they ask, "Why are you getting the cyclosporine level?" How significant is the level at that point in time? If the serum creatinine starts to go up, then clearly the physician must measure the serum cyclosporine level. If the person develops tremors, get the level. If you're worried about subtherapeutic levels, you can get it. In general, however, the significance of long-term follow-up on cyclosporine levels is not so clear.

Question: If you have to use an antihypertensive drug, which class do you use?

Appel: I'd love to give anti-endothelin antibodies, which, of course, are not available. Of the drugs that you could use, in general, even though there is the interaction, I would use a calcium channel blocker, and I would lean to nifedipine, because it does not clearly increase the levels of cyclosporine and because I think it is very effective. In general, I try to keep away from the ACE inhibitors, for fear of exacerbating hyperkalemia, which is a common side effect of both ACE inhibitors and cyclosporine; using them in combination virtually guarantees significant hyperkalemia.

Lichtiger: I wanted to ask you this, Jerry. There is literature from the NIH about prevention of renal toxicity using fish oils, using bromocryptine, and even more recently some data on verapamil. That's why I was interested in why you said that you would use nifedipine.

Appel: Right. On protection from toxicity, a lot of studies are ongoing, none conclusive. The most recent data still shows we cannot clearly protect against nephrotoxicity. There are two big potential areas of interest here. The first area is the calcium channel blockers, which have been shown to be helpful in preventing nephrotoxicity, usually of the acute type—drop in glomerular filtration rate during the initial weeks or months. That form of nephrotoxicity is usually acute and reversible.

The more important issue is chronic nephrotoxicity. Nobody knows if the short-term effect leads to the long-term effect. That is really the question. If you can reverse the decrease in glomerular filtration rate, will you prevent chronic renal injury? We do not yet know. Clearly, using low-dose short-term therapy should be beneficial here.

The author of the final contribution to this symposium has shown us new ways of thinking. Building on more than four decades of basic and clinical research and clinical practice, Dr. Janowitz has recently begun asking new kinds of questions—questions about the natural history of disease, questions about placebo lessons, questions about assessment of therapeutic gain. He discusses assessing therapeutic efficacy. How well does anything work? As one assessment of efficacy, I might just point out that Dr. Janowitz, Clinical Professor of Medicine Emeritus and Consulting Physician at the Mount Sinai Medical Center, is responsible for about 30% of this symposium's faculty having become gastroenterologists.—DBS

Assessing Therapeutic Efficacy:

How Well Does Anything Work?

Henry D. Janowitz, M.D.

My colleagues Asher Kornbluth, Peter Salomon, Henry Sacks, Samuel Meyers, and I have for some time been trying to extract some meaning from the literature on therapeutic trials in inflammatory bowel disease (1–3). Allow me, however, to make a comment as not only the oldest participant in this symposium, but also one who approached inflammatory bowel disease at a time fifty years ago when physicians had just stopped instilling aquaflavin and gentian violet into the colon through appendicostomies or cecostomies: I cannot help wondering, as I hear about this new panoply of drugs, whether we really aren't trying to pour old wine into new bottles.

The names from my own time remain the same, but the players change categories. Nonabsorbable sulfonamides and intestinal antibiotics were replaced by sulfasalazine, and sulfasalazine by metronidazole; now broad-spectrum antibiotics are being replaced by antituberculosis drugs. Sulfasalazine became mesalazine. The immunosuppressives (cortisone and ACTH) were replaced by azathioprine; betamethasone was replaced by tixocortol pivalate and the other rapidly cleared steroids discussed by Derek Jewell.

Azathioprine moved back to the "old" wine list; 6-MP became the new wine; 6-MP became the old wine; cyclosporine became the new wine. Where is MK507? We have the immunomodulators hydroxychloroquine and omega 3 fatty acids, and now the leukotriene inhibitors will soon appear. Maybe we will go on to treating the mucosa by installing short-chain fatty acids.

We all want to know whether the drugs we use are effective. We certainly know now, I think, that it is better to use a real drug than a dummy drug. But the question is, how much better? We want to know that, and our patients want to know what their chances are of responding to a drug that we are going to give them. And, if they do respond, how long will they stay well? So we cannot get away from going back again to look at the natural history of the disease.

At present, since everyone gets treated, the only way I can see of learning anything new, short of declaring a moratorium on all therapy, is to go back to the placebo studies.

The question of ulcerative colitis is what I primarily consider here. We chose to look at ulcerative colitis because it seems to be easier to extract from the literature the information we are looking for. Secondly, I have the impression that in the era of immunosuppressives, especially steroids, and 5-ASA and its relatives, we have all acquired an air of complacency regarding the effectiveness of our therapy for ulcerative colitis. So at the risk of being didactic and repeating what we all know, we looked at 11 controlled trials in ulcerative colitis, which included 185 patients, including 19 of our own. Most (182) had

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Adapted from the author's presentation at the seminar "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" held at The Mount Sinai Medical Center, December 8, 1989. From the Department of Gastroenterology, The Mount Sinai Medical Center. Address reprint requests to Henry D. Janowitz, M.D., at Box 1069, One Gustave L. Levy Place, New York, NY 10029.

mild to moderate disease; only 4 of 5 had severe conditions. Patients were studied by endoscopic, pathologic, and clinical criteria, and followed up for from 15 to 42 days. This is the best that we could get out of the current literature. The study patients were receiving only placebo therapy. Up to 52% improved and remitted clinically, and up to 59% improved sigmoidoscopically. However, relapses occurred quickly, within two months of the so-called spontaneous improvement.

In six maintenance trials of 174 patients in remission, receiving only placebo therapy (134 followed up for 6 months and 40 for 12 months), up to 51% remained in remission. Favorable predictive factors for continued remission included normal rectal mucosa on sigmoidoscopy, limited extent of colitis, and remission that was recently achieved by active therapy or maintained by therapy for at least one year prior to entry into the study.

What is the situation in relation to Crohn's disease? Nine controlled trials with 384 patients, three of the controlled trials in patients with active disease; the remainder of patients in remission. On the average, these patients were treated for approximately 4 months. Twenty-six percent to 42% of these patients went into remission. In the recent study from Denmark and Canada reported by Jorn Brynskóv, in the 3-month study 34 patients were followed up for 3 months on placebo, and 32% went into spontaneous remission. From this paper it seems that the favorable factors were no prior therapy, especially no steroids; mild disease; recurrent disease after surgery; small-bowel disease; and no perianal disease. The odds were in the patients' favor; they had a good chance of doing well even if they received the dummy drug.

What about the maintenance studies of patients in remission? In six studies, 193 patients were followed up for from 6 months to 4 years. Apparently, if a patient with Crohn's disease goes into a remission, he or she has a pretty good chance of remaining in remission, because 75% of these patients remained in remission for one year if they went into remission at the time they entered the study, and 63% remained in remission for a second year.

In a recent, at this time unpublished, Canadian-European study that Allen Thompson has shown me of 103 patients in the control arm in remission for Crohn's disease, either following any form of medical therapy or resection, and followed up for one year, 64% remained in remission in the placebo group. The favorable factors seemed to be remission following a recent exposure to steroid therapy and small-bowel rather than large-bowel disease.

Therapeutic Advantages

With this as a background, what can we attempt to say about the therapeutic advantages, as we have termed it, or the therapeutic gain, as Brynskóv terms it? The trendy word, of course, is "metaanalysis." Whether we like it or not, we gastroenterologists are going to have to become familiar with metaanalysis, and one of the new gastrointestinal journals is going to have a section on metaanalysis. Fortunately I do not have to worry about the software programming, but apparently the mathematical transformations of combined controlled trials have been worked out fairly well by Thomas Chalmers and his group, and we are glad that Henry Sacks is helping us with this task.

One would of course have to factor into any study of therapeutic advantage the therapeutic disadvantages each drug carries with it which prevented those who entered the study from completing it. What is the story at present? We thought we would first look at patients undergoing single-drug treatment in an effort to at least get some secure data before we dealt with the problem of multiple drugs. Despite 30 years of treating ulcerative colitis, we found 11 placebo-controlled single-drug trials in patients with mild to moderate disease, no studies of patients with severe disease (I do not think any placebo studies are likely in that group ever), and 5 studies of patients undergoing drug maintenance therapy.

We're thus talking now about active ulcerative colitis, mild to moderate. Eleven placebo-controlled trials in 363 patients were conducted for anywhere from 15 to 40 days, in which clinical and sigmoidoscopic improvement or remission with the drug were compared to placebo.

The *therapeutic advantage* of the drug compared to the placebo ranged from 37% to 38%.

Among individual therapeutic modalities, sulfasalazine, 5-ASA and its analogs, or olsalazine, sulfasalazine, or its analogues given by enema, hydrocortisone enemas, prednisolone enemas, prednisone enemas, and prednisone by mouth, the overall therapeutic advantages were similar. No single drug was superior to the other.

What about maintenance of remission in ulcerative colitis? Five trials were carried out on about 350 patients, with sulfasalazine, olsalazine, prednisone by mouth, and cromolyn, a drug that has appeared, disappeared, and may be in for a revival again to prevent the degranulation of mast cells. Overall, remission was 70% on the drug as compared to 45% on the placebo; the maintenance therapeutic advantage of the drug compared to placebo was 31% in 6 months, and 46% in 12 months, with no advantage for prednisone.

A point to be remembered here is that in maintenance of remission in ulcerative colitis, things did improve if the patient was taking the real drug compared to the dummy as time went on. Where at 6 months there was not much difference (a gain of only 19% if the patient remained on the drug), at the end of 12 months the gain was at least 44% if the patient continued to take the drug as opposed to the placebo.

But after 30 years, we cannot yet predict on admission how this group of (mild to moderately severe) patients will respond on the basis of whether it is their first attack or a relapse, or how long they have been in this relapse, or what the extent of their disease is. A lot of patients have been treated with a lot of drugs for a long time. Rarely has so little been gained from so much effort.

On the question of patients who receive more than one drug, we are in a welter. Pulling out just one of these studies (my colleagues and I have not gotten too far on this question), the classic study of Truelove and Witts: whatever drug the patient was on before, and in many it was sulfasalazine, it was continued during the trial when cortisone was added. The best results occurred in the mild cases and in the first attack: 60% of their patients responded, 40% to placebo. The therapeutic advantage in that classic study was only about 20%.

What are we going to do about trying to assess the efficacy of our current drugs in severe or fulminant ulcerative colitis? In our own study of 66 patients, really severe and fulminant ulcerative colitis by Lennard-Jones's criteria, we conclude that the subgroup that had been taking steroids did not respond as well to ACTH as they did to hydrocortisone. Overall, 42% of the patients achieved remission. The best results in this study of 66 patients with severe fulminant ulcerative colitis ranged between 53% and 63%.

Another way of approaching severe fulminant ulcerative colitis, since we are not going to have any controlled trials, is to consider Truelove and his associates and Jarnerot's "atomic blast" therapy.

Truelove: 5 days, intravenous steroid, antibiotics, 5-ASA or sulfasalazine, and steroid enemas. A hundred trials in 87 patients with remission in 60%, 40% going on to surgery. The advantage of the therapy was 20%.

Jarnerot's study, not quite so dogmatic as to the day of surgical guillotine: 62 patients treated with a similar program; 47% did not go to the operating room, 50% did.

How would you calculate the therapeutic advantage?

All the papers that I have seen on meta-analysis, in whatever field, say that what we need are better studies on inflammatory bowel disease. We are going to continue trying to extract from the literature in this kind of metaanalysis the current results on publications on Crohn's disease, but obviously that is going to be a much harder job than in ulcerative colitis, hard as that is.

Questions and Answers

Sachar: Dr. Janowitz, let me ask you about your view on perhaps a more optimistic way of looking at remission maintenance data. You've given an example of studies where on active drug, remission is maintained in 73%, versus 51% on placebo, and you say that's only a 22% therapeutic gain.

But suppose we look at it from the point of view of the probability of relapse. On active treatment 27% relapse, on placebo 50% relapse. So we've cut the probability of relapse in half. Or if we take the more classic Dissenayake paper on 3-g sulfasalazine, it's a 44% maintenance of remission on placebo and 86% maintenance of remission on active drug on sulfasalazine. You would say, the therapeutic gain is 42%. Not bad. But if we talk about the probability of relapse, we're saying that on active drug the probability of relapse is only 14% instead of 56% on placebo. We've cut the probability of relapse to one-quarter of what it otherwise was.

What's the right way of looking at that question?

Janowitz: I wouldn't want anyone to think that I was a dummy doctor and wanted to treat my patients with dummy pills. I certainly think that we have shown that our drugs are more effective than the placebo, and they do confer varying degrees of advantage, both in the acute phase, especially, and in the maintenance phase.

It has always irked me that no drug effective for Crohn's disease had been shown to be effective in controlled trials in maintenance. If we're doing the same thing in both diseases, suppressing the ongoing inflammatory process, I find it difficult to accept the results of national controlled trials. So I'm relieved that anomaly has been removed.

I think that 5-ASA will offer a modest degree of protection against relapse in maintenance studies in Crohn's disease as it does in ulcerative colitis when studied against placebo. We now look forward to the continuing followup of the immunosuppressive agents in these diseases.

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The lecture presented here was the sixth annual Alexander Richman Commemorative Lecture in Humanism and Ethics in Medicine, a lecture series that is a component of the ethics program at the Mount Sinai School of Medicine. Just before this lecture, the 1990 Alexander Richman Commemorative Award for Humanism in Medicine was given to Donald Gribetz, M.D., citing him as a pediatrician's pediatrician who has also for many years been a leader in bringing to the surface questions of medical ethics arising from the Jewish and Biblical viewpoint, particularly by organizing a series of successful symposia on Jewish medical ethics. Elie Wiesel refers in his talk to Dr. Gribetz.

Urgent Ethical Questions Today

ELIE WIESEL

THE SUBJECT of ethics, of urgent ethical issues today, of course appeals to me. But especially discussing it here [at the Alexander Richman Memorial Lecture in Humanism and Ethics] appeals to me because it appeals to you, ladies and gentlemen. I'm attracted by your commitment to ethics. I have been campaigning for compulsory ethics courses in universities for years and years, without much success. I would go, I still go, from college to college, university to university, trying to convince all of their presidents and deans that it is absolutely imperative for students not only to study science or medicine or engineering. They must know what the whole thing is about, and the whole thing is about other human beings, in other words, ethics.

Now something strange has happened to me. In all the places where I advocated ethics courses, I had no success. Here, where I have never done anything, there *is* an ethics course.

Two points on the subject. Why is ethics imperative? Not because it gives you certainty. Quite the opposite—because it prevents you from having certainty. Certainty causes bigotry and fanaticism. Fanaticism exists not only in politics and in religion, but also in the sciences, in literature, in education. I know that you know that a fanatic is someone who is always sure of himself or herself. A fanatic is a person who believes that his or her word is the only word, his or her truth negates all other truth. A fanatic actually is convinced that he or she knows more than God, who surely is not a fanatic. A fanatic, in my view, actually holds God prisoner, and therefore an ethicist, as we call people who believe in ethics today, is not only freeing himself or his fellow human beings, he is also freeing God from the fanatic's prison.

The moment you introduce ethics, it means that there is a certain hesitation, a moment of hesitation. Life is not made of years. Better than anyone else you who practice medicine know that life is made of moments. André Malraux used to call these moments privileged moments, *les moments privilégiés*. And there are very few in one's life. Usually they have to do with turning points, they have to do with other people's concerns or emergencies, and they have to do with the fact that you, that each of us, in moments of grace, can influence the life or the future of another person, whoever that person may be. Hesitation is offering a possibility to enter, together with your patient, together with the other person, whoever that person may be, into a common quest. Now you examine the person, that person is waiting. That person is waiting for your judgment just as a prisoner is waiting for his release. And if you are aware of that, then instead of causing anxiety, you will relieve him or her of that anxiety by sharing, by sharing in a certain way. That is ethics.

Of course, I know that it's easy for me to say that. I'm not a physician. But I have been a patient. And I speak from the viewpoint of a patient. I can tell you that a doctor to a patient not only is all-powerful, a doctor to a patient is a mes-

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Adapted from the author's Alexander Richman Commemorative Lecture at The Mount Sinai Medical Center on March 29, 1990. The author is Andrew W. Mellon Professor in the Humanities at Boston University and a member of the departments of religion and philosophy there. He received the Nobel Peace Prize in 1986. Address reprint requests to the author at 745 Commonwealth Avenue, Boston, MA 02215.

siah. Everything depends on the way you look, on the way your face looks—is it gray or pale? Are you worried? Are you not? When I was a student in Paris, I must tell you, I was not, and have never been, attracted to medicine. Never, because I'm a coward. I couldn't see blood. When I get an injection, a shot, I look away. However, I was attracted to philosophy. Why? Because of the questions. I left it because of the answers.

I only believe in questions. There is quest in question. And of course, as a philosopher, a student of philosophy or literature, I believe in the quest. The word ethics—in Hebrew *musar*—really means to offer, to share, to transmit. For me to transmit, there must be someone who receives. In other words, ethics negates isolation. You cannot be ethical if you are alone, and you cannot be ethical if you leave anyone alone. The answer to solitude really is ethics. A patient can be alone. You physicians can be alone, when you have certain questions to resolve, and you know that whatever the solution is, it is painful.

Recently, I heard of such extraordinary questions in medicine that I started to regret I wasn't a physician. I thought that philosophy has more questions than medicine. I see now it's not so. Medicine now faces more questions than philosophy does. The extraordinary problems that doctors have to face—what to do, as you told me, if a mother has AIDS and she is pregnant, because if you try giving her treatment, the child may suffer. Whom do you consider worth saving—the child or the mother? What do you do with unborn children or just-born children suffering from Down's syndrome, from other diseases? How do you deal with a patient who has cancer—do you tell the patient? If so, when?

I am not sure I have the answers. I believe in truth, and I believe that patients deserve the truth. I also know that some patients cannot take the truth. I know it from personal experience.

I had a sister, and she survived the war. One day I was in class teaching at City College when they called me out and my brother-in-law, who is a doctor, told me that they discovered cancer, but she didn't know it and they didn't tell her. And it was all right. She went to doctors, she got therapy, chemotherapy, radiation, and she did all right. And then she heard of a very special specialist, an oncologist, and she went to see him. He was someone who believed that no matter what, you must tell the truth. He told her the truth; she died a few weeks later. She couldn't take it.

So what do you do with your commitment to truth, and with your commitment to life? I would like ethics to mean that, at such a moment, at that moment, you hesitate. You don't go straight to the given answer. No one has the answer. As a patient I know the doctor has the answer, as a human being I know that no one has it. We are all, after all, vulnerable, weak, frail, human. In Yiddish you say, *On dos oich nit,* not even that—you must be a human being before everything else.

In other ways, the question may go further. Whom do you treat first? Today, when "ethics" has become more than just a word, I would say it has become fashionable, but the word "fashionable" has a certain connotation, and I mean it to praise—in Hebrew, we say *li'sh'vach.* It's good that we are obsessed with ethics. It means human rights, it means being involved, it means to listen. But what do you do first? Where do you start?

I heard a marvelous story about a close friend of mine, Abraham Joshua Heschel. He wasn't my teacher, my teacher was his opponent Prof. Saul Lieberman. But Heschel was my dear friend. I heard a great story about him from a student of mine who had been his student, too. His student, who became mine, told me that when he applied to the Jewish Theological Seminary, he went to Heschel, the dean of admissions. He came to the interview trembling; after all, students tremble at such interviews. And Heschel asked him certain questions, and then Heschel said, "Tell me, young man, what did you do this morning?"

"Professor, I got up in the morning, and I couldn't even drink coffee, I was so nervous, I came to see you."

"And what did you *do* this morning?"

"Professor, I told you. I came."

"Where do you live?"

"116th Street."

"Really." (The Seminary is on 125th Street.) "Tell me. You came to see me. How did you come?"

"I was waiting for the bus. There was no bus, I was running."

"And what did you see?"

"Nothing. I was running."

"And you didn't see that on 116th Street there is a kiosk, a newsstand, there is a man who waits for customers impatiently? You didn't see at 118th Street there is a Korean who sells vegetables? Did you know he has a daughter, and the daughter is there helping him? And you didn't see that further down, there is a cobbler, there is a man waiting for his shoes. . . . And you want to be a rabbi?"

A rabbi who doesn't see? A doctor who doesn't hear? Before anything else you must hear and see. Once you start seeing and hearing you are in trouble. Because too many people wait for you. Too many people need you. Where do you start? My students occasionally ask me this question. I push them to be involved, to do things. And they want to know: But where do we start?

There are so many places where people are in danger. Where do you go now? Do you go to Hong Kong because, scandalously, outrageously, boat people are being sent back to Vietnam? And we say nothing? We in this country say nothing that people are being sent back home, to Vietnam? We who should remember the story of the *Saint Louis,* the German ship that was sent back from U.S. shores to Nazi Germany with a thousand Jewish refugees aboard?

Or should we perhaps go to Rumania, where there are children . . . I saw the pictures, my God, if I were a doctor, believe me, I would leave everything and go there. I'm serious. Those poor, poor children, children with AIDS, who were hidden by this arch-murderer Ceaucescu: Should you go there? Right away?

Or should you go maybe to Armenia-Azerbaijan? Should you go to Asia, where still 12 million children die every year? I say these words, and I must tell you my heart breaks—12 million children. And we do nothing, except from time to time we shed a tear?

Of course my priorities as a Jew—I must say so honestly—are Jewish priorities because I belong to a traumatized generation, a generation that knows that sadness has a past which hope does not. So in a way, when I see something sad it evokes fears of darkness, where there are promises and promises.

But my priorities are not exclusive. As a Jew I must try to help Soviet Jews, yes. I remember when Donald Gribetz came back from his trips to Russia in the 1970s. I remember the pictures—that's when I became involved in helping Vladimir Slepak, because of Donald. And the Jews in Yemen—all of a sudden we discovered 2,000 Jews in Yemen who suffer atrociously daily humiliations. I have documents written in marvelous Hebrew from Yemen. One man wrote me an astonishing letter in which he said, I am ready to sell everything I possess to get back my wife. The local caliph fell in love with his wife and stole her. There are dozens of cases. And we don't even know about them.

What about Jews in Syria who are in jail? Again, I see, I try to see other people, other tragedies. How can one not see those tragedies? And you wonder, where do you begin helping?

The answer is, start anywhere. Anywhere. My experience has been that those who help one cause end up helping all causes. I always meet the same people at philanthropic functions. One is for this cause, one is for that cause, but somehow they are always there, the same people are there. So start anywhere. In your case you start at home, the patients who come to see you. However, while examining the patients and saving their lives, which is a unique privilege, think of those who are not there, who cannot afford you. Those who live in the jungle, those who live far away from civilization. After all, ethics is what makes a civilization civilized.

We must deserve to belong to our generation, a special generation, really, a very special generation. No generation in history has received as many dreams of fire, as many sparks of hope. Your parents have been alive during the worst tragedy in history, and yet they have seen and you are witnessing a great renaissance for the Jewish people, and for the whole world. Oncologists try to tell me that more progress has been made in the last seven years than in centuries in the field of cancer research. The same is true in general medicine and in surgery. I had an accident when I came to America, and I was laid up for a whole year. Everything was broken, my hip, everything . . . a taxi ran over me, so for a whole year I had surgery after surgery. Today I know it will take you three weeks to replace a hip or to replace a knee. So you are doing things because things have been given to you: the privilege, which one must be worthy of.

Now, at the same time, one cannot forget that your field has been abused. Medicine has been abused in the past. In my own lifetime. Those doctors who became criminals, who used medicine to mutilate, to stifle, to humiliate human beings simply because they were Jewish—those doctors brought dishonor to your profession and to your calling. But don't think that you can simply go on doing what you are doing without thinking of how that was possible. How was it possible? Now, when you think of those doctors, you realize that what was missing was the ethical component. But you also realize that ethics, too, could be corrupted. Those doctors were convinced they were ethical. They were convinced that they were doing the right thing in killing. They were convinced they were just.

So where is ethics? Even the word must undergo an examination. Even the idea of ethics, the concept of ethics, must be reevaluated. To me, coming from a Jewish tradition, I believe that in my tradition, ethics simply implies "the other." Look at the other. Or in a different way, on a higher level, look to the victim. Always listen to the victim. The victim deserves to be heard. If the victim says that he or she suffers, believe. If the victim needs your help, believe. It is the victim who possesses a fragment of truth without which no ethical attitude could be complete.

Today I heard from you, Donald, a very poignant question: what to do with a patient who for religious beliefs refuses blood transfusion? It is an extraordinary question. I read about it occasionally in the papers but it only recently hit me. What do you do? Actually, the question is, does that patient have the right to commit suicide? Slow suicide, but suicide. And here we enter, of course, a field you too must be aware of, and I would like you one day to give me the answers.

I am sure you physicians or psychiatrists will agree that a person who goes through extreme pain and then survives that pain is on the edge, on the threshold of falling prey to insanity. Logically that person should be exposed to the universal insanity which he or she surely had absorbed during the time of the trial and the Nazi persecution. How do you explain that so many—so many, perhaps not so many—survived, and that among those who did survive that tragedy, you do not find that many mental cases? Somehow they adjusted. I don't know how, but they did. They got married, they had children, usually marvelous children; their children are extraordinary.

Do they have nightmares? Yes. They don't talk about it. Do they remember? Yes, but from there to say that they are unbalanced mentally—no. Here and there, there must be disturbing cases, but usually, I would say, they remain normal. And their normalcy fascinates me. What is the answer? So much was done to them and against them during the war and after the war. They were treated like poor cousins after the war: They were humiliated by their own people. People didn't want to hear, to listen, to see. And yet they somehow remained noble citizens of society, dutiful sons and daughters of their people. How did they manage?

I feel it has to do with ethics. They came, maybe subconsciously, to a realization that it is not your fault that others did wrong to them. Why punish you with my mood, with my despair, if some killers have attempted to exterminate our people? Why? That is the ethical presumption that I attribute to them. Seneca, the great Roman writer—he was anti-Semitic, but who wasn't then? Even Cicero was—Seneca said that the Roman empire declined the moment its victims, the defeated, brought with them a morality, an ethical conduct, an ethical ideology, an ethical philosophy that was superior to the Roman morality. Seneca watched as the Romans brought the young Jewish warriors from Judea, and he made them march under the Arch of Titus, called the Arch of Triumph; with the inscription "Judah capta" he finally managed to vanquish Judea and capture its defenders. Seeing these young lions from Judea, Seneca realized that they were defeated but their morality was not. That day, he decided, Rome was finished. Subsequently, he committed suicide.

Our society has a chance, and our society now is being tested. After all, we are now entering the last decade of the century, the last century of a millennium; events are going so fast they make you dizzy. History has accelerated its pace to a degree never known before. It's a very privileged situation, and it's a very privileged generation that endures it and lives it. But one thing is clear to me. If we want our legacy to be transmitted to the 21st century, it must be a legacy not of fear and surely not of suspicion.

Suspicion means hatred, and hatred means racism and anti-Semitism and all the antihuman instincts that a person is capable of. The legacy must be a legacy of humanity, a legacy of compassion—in other words, it must be an ethical legacy.

Intraoperative Management of Fluids in Neurosurgical Patients

MICHAEL M. TODD, M.D., ALLAN P. REED, M.D., AND IAN H. SAMPSON, M.D.

TRADITIONAL fluid management of neurosurgical patients is based on both clinical experience and well-entrenched but unsubstantiated beliefs (1). Recent studies, performed largely in animal models, suggest new concepts for consideration. Although much of this article pertains to animal work, attempts will be made to draw clinically relevant parallels. The question we have been asking is, "What is the influence of osmolality and colloid oncotic pressure on the formation of cerebral edema in the neurosurgical patient?" We have attempted to determine whether crystalloids, such as lactated Ringer's and normal saline solution, promote the formation of cerebral edema.

The standard approach to fluid management in neurosurgical patients with head injuries or brain tumors has been to avoid "overhydration" with crystalloid solutions. Colloidal plasma expanders are generally recommended until blood is available. One of the goals in the management of neurosurgical patients is to "keep them dry" to promote shrinkage of intracranial volume. However, dehydration and hypovolemia have a negative impact on hemodynamics and conflict with anesthetic management. Treating the decreased systemic blood pressure resulting from negative inotropic and vasodilating effects of general anesthetics requires volume expansion, an option that traditional wisdom has shunned. The best explanation is that patients receiving several liters of crystalloid solution, for laparotomy, develop peripheral tissue edema, as evidenced by swollen eyes, arms, and legs (2). Although undocumented, the assumption has always been that peripheral edema must be accompanied by some degree of cerebral edema (1). The crux of fluid management for neurosurgical patients is based on this assumption. In an effort to elucidate the influence of fluids on the central nervous system and the cardiovascular system, we conducted a series of experiments directed at the intricacies of fluid management.

Effects in Normal Blood-Brain Barrier

Formation of Peripheral Edema. Starling's law, which dates back to 1892, describes the net movement of fluid across a vessel wall (3). An outward hydrostatic pressure is opposed by an inward pressure due to the presence of large, colloidally active molecules. Under most circumstances, hydrostatic forces are slightly greater than oncotic forces, resulting in a net leakage of fluid into the interstitial space which is cleared by lymphatic drainage. Reducing colloid oncotic pressure (COP) by the administration of large amounts of crystalloids allows more fluid to accumulate interstitially. Eventually, interstitial fluid accumulation will exceed the ability of lymphatics to clear it, and peripheral edema develops. Since large-volume crystalloid infusions are often associated with a fall in normal COP, their administration can lead to peripheral edema.

Formation of Brain Edema. Evaluation of brain edema remains difficult. Isolating the effects of COP on brain edema further complicates the issue. Numerous experiments have been performed in which large volumes of crystalloid solutions have been infused into intact animals (4–7). Such models can produce high pressures in

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From a Grand Rounds in Anesthesiology presentation by the authors at The Mount Sinai School of Medicine, September 20, 1989.

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the right side of the heart, central venous system, and cerebrum. As defined by Starling, increasing hydrostatic pressures can produce brain edema independent of other factors, and several experiments have demonstrated that increasing cerebral venous pressures, particularly in the presence of an impaired blood-brain barrier, can produce edema (8). The correct experiment should thus maintain hemodynamics constant during the alteration of plasma composition.

Given these caveats, a rabbit model of isovolemic hemodilution was devised (9). A solution of either crystalloid (lactated Ringer's solution) or colloid (6% hetastarch, [hydroxyethyl starch]) was infused as the test fluid. Arterial blood was withdrawn at a rate of 2 mL/min for 1 hr. In the group receiving lactated Ringer's, the animals received 400–500 mL of fluid (the human equivalent of about 7 L), whereas the group receiving hetastarch required 125 mL to achieve isovolemic hemodilution. In both groups the hematocrit started at approximately 43% and decreased to approximately 20%.

Intracranial pressure (ICP) measurements in these rabbits seemed to confirm the conventional wisdom. There was a small rise in ICP in control animals (which received only maintenance fluids) as well as in those receiving hetastarch, but animals receiving lactated Ringer's had a much greater increase. We initially assumed that the increased ICP resulted from cerebral edema.

Measurement of Cerebral Water. Measurement of cerebral water content is generally performed in one of two ways. The easier method involves comparison of tissue weights prior to and after drying. The difference between the wet and dry weights is the water content. This method can be used with great accuracy but is difficult to apply to small pieces of tissue. With smaller specimens a technique called microgravimetry is used (10). A graduated cylinder is filled with a kerosen-bromobenzene mixture to produce a linear density gradient. The specific gravity at the bottom of the gradient is approximately 1.060 and the specific gravity at the top of the gradient is about 1.020. Samples of tissue, 10–30 mg, are placed in the solution. The tissue sinks until it reaches the level of its own specific gravity. Since water has a specific gravity of 1.000, as the water content increases, the tissue samples float higher and higher in the gradient. This is a sensitive, precise, and relatively simple method of measuring water content.

These techniques were applied to our lactated Ringer's versus hetastarch experiments. Higher water contents were found in the crystalloid group compared with the colloid and control animals. The findings from these measurements again seemed to suggest that administration of large amounts of lactated Ringer's produced cerebral edema.

However, more detailed analysis revealed a potentially confounding variable: a fall in serum osmolality was seen in the lactated Ringer's group but not in the hetastarch or control animals. This change seemed to be related to the composition of lactated Ringer's. The calculated osmolarity of lactated Ringer's is about 273 mOsmol/L. Since normal serum osmolality is about 285 mOsmol/kg, lactated Ringer's appears to be only slightly hypotonic.

But the terms "osmolarity" and "osmolality" are not interchangeable (11, 12). Osmotic pressure depends on the number of independent particles contained within a solution. Oppositely charged particles within a solution tend to attract one another, forming a single particle where two previously existed. Hence, in most salt solutions, measured osmolality is less than calculated osmolarity. The measured osmolality of lactated Ringer's is approximately 250 mOsmol/kg. Consequently, lactated Ringer's contains approximately 35 mOsmol/kg less than normal serum and is therefore more hypotonic than we initially appreciated.

In fact, each liter of lactated Ringer's contains approximately 100–110 mL of free water, and the administration of 10 L of lactated Ringer's to a normal patient is the equivalent of infusing about 1 L of 5% dextrose in water. Since most neurosurgical patients come to the operating room in a dehydrated, hypertonic state, 1 L of lactated Ringer's may contain as much as 210 mL of excess free water (relative to the patient's baseline). Consequently, contrary to popular belief, lactated Ringer's is not an isotonic, isoosmolar fluid. Therefore, the fall in osmolality seen in our initial work with rabbits may have been due to excess free water administration.

The crucial issue is whether or not changes in brain water content and intracranial pressure are truly the result of the observed 4 or 5 mOsmol/kg fall in osmolality.

To answer this question, the hemodilution model used earlier was discarded in favor of a plasmapheresis system in which hematocrit and intravascular volume were maintained constant (13). Blood is removed, and red blood cells are returned to the animal along with one of several plasma replacement fluids. The process can be performed continuously using hollow fiber plasmapheresis filters, or discontinuously by removing blood, centrifuging it, and reinfusing the red cells.

In our first plasmapheresis study, hollow-fiber filters were used (13). In this particular trial, lactated Ringer's was not employed, but plasma replacement fluids were specially designed to carefully control osmolality and COP. Three groups, each receiving a different fluid, were assessed. The hypoosmolal group received a solution containing normal COP (20 mmHg) created with hetastarch, but with an osmolality of only 111 mOsmol/kg. The hypooncotic group received a solution with a COP of 0 and an osmolality of 308 mOsmol/kg (calculated on the basis of preliminary experiments to maintain plasma osmolality constant during the study). The isooncotic/isoosmolar group received fluids such that both COP and osmolality remained constant. After 1 hr of plasmapheresis, analysis of both gray and white matter specific gravity revealed no difference between the isooncotic/isoosmolal group, and the hypooncotic group. However, in animals rendered hypoosmotic, there was a large increase in brain water content.

In short, although there was obviously an important osmotic effect, no oncotic effect was demonstrable.

To carry these experiments one step further, a rabbit cardiopulmonary bypass model was devised by Brad Hindman at the University of Iowa. The experiment utilizes a membrane oxygenator, a small reservoir and a 300-mL circuit. Initial trials compared a saline and a hetastarch prime. As expected, the saline prime reduced plasma COP from a value of approximately 20 mmHg to about 5 mmHg. By contrast, there were no COP changes in the hetastarch group. As in the earlier studies, there were no differences in brain water content between the saline and hetastarch groups, in spite of the differences in COP. Simultaneous analysis of peripheral tissue (muscle) water content revealed a large increase with the saline prime. In other words, there was peripheral edema associated with a reduction in COP but no cerebral edema.

Effects in Altered Blood-Brain Barrier

Although fascinating, these experiments do not address one critically important issue relevant to neurosurgical patients: they were all performed in animals with a normal blood-brain barrier. By contrast, many disease states of interest are associated with damaged blood-brain barriers. To investigate this aspect, a cryogenic brain injury model was selected. Evan's blue dye, an albumin-bound substance, was injected intravenously and liquid nitrogen was briefly applied to the left side of the rabbit skull. The underlying tissues were frozen, cells were damaged, and the blood-brain barrier was disrupted, as evidenced by the extravasation of dye.

Using this model, the studies described above were repeated (14, 15). One group of rabbits received maintenance fluids only; two groups underwent isovolemic plasmapheresis using either isotonic saline or isotonic 6% hetastarch. Hetastarch is a synthetic starch molecule resembling glycogen. It is clinically available as a volume expander and is supplied in normal saline. The average molecular weight of the mixture is 69,000, but some particles may approach 1,000,000. After approximately 1 hr of plasmapheresis, the brains of the rabbits were removed and the water content of representative areas was assessed by microgravimetry. As expected, water content (edema) decreased as distance from the cryogenic lesion increased. However, there were no differences between the experimental groups.

In addition, the data were subjected to regression analysis on a section-by-section basis (all groups combined). The results indicated that changing colloid oncotic pressure had no influence on the water content anywhere in the brain. By contrast, manipulating osmolality altered the water content of only the normal brain regions. In the vicinity of the lesion, there were no relationships between changes in either COP or osmolality and water content. This finding corresponds with experiments dating back to the 1960s, which demonstrated that the administration of compounds such as urea or mannitol to animals with similar lesions reduced *normal* brain water content, but did not alter water content in the vicinity of the injury (16–17).

One problem with this experiment is that the 2-hr time period between production of the cryogenic lesion and killing of the animals may have been insufficient to allow equilibration between intravascular and extravascular fluid spaces. To eliminate this potential problem, an 8-hr reevaluation period, following plasmapheresis, was employed in the next series of experiments (18). Both isooncotic and hypooncotic groups were used. The COP diminished to about 10 mmHg, whereas osmolalities remained constant throughout the duration of the experiment. Over the 8-hr period, intracranial pressures were identical among the groups, and no differences in regional water content could be attributed to the fluids administered. Nevertheless, simultaneous increases in duodenal and muscle water indicated an increase in peripheral edema associated with a decrease in colloid oncotic pressure.

Differences in Dynamics of Peripheral and Central Fluid. These results seem to differ from those predicted by Starling's law. Although fluid shifts in the periphery follow the Starling hypothesis, the brain appears to act differently. Infusion of large amounts of crystalloid produces peripheral edema, but not cerebral edema. The difference between peripheral and central fluid dynamics may emanate from the differences in peripheral and brain capillary structure.

Peripheral capillaries contain a multitude of pores which permit essentially free passage of small molecules such as sodium, potassium, chloride, bicarbonate, and others. By contrast, large colloidally active molecules such as albumin do not cross easily. In order to move water across a membrane in response to changes in COP or osmolality, a concentration gradient for the solute must exist. The high permeability of peripheral capillaries to small molecules allows their equilibration across the membrane, thereby preventing the formation of a gradient. In contrast, large molecules cross poorly and, hence, it is possible to establish an oncotic gradient. Manipulation of the plasma concentration of these large molecules can therefore alter fluid dynamics.

In contrast, capillaries in the brain possess tight junctions, the blood-brain barrier. Consequently, neither large nor small molecules readily traverse brain capillaries, unless they are highly lipid soluble. Therefore, a change in the concentration of either can alter the transmembrane osmotic or oncotic gradient. Because there are so many more small molecules (ions) than large molecules (proteins), the intravascular concentration of small molecules becomes the dominant factor in determining brain fluid movement (4, 16, 17, 19–24). Since a 1 mOsmol/kg gradient produced by a change in small ions is equivalent to approximately a 19 mmHg hydrostatic pressure gradient change, even a major change in COP of 8–10 mmHg is equivalent to only a 0.5–1.0 mOsm change in total osmolality. In other words, the presence of an intact blood-brain barrier drastically reduces the importance of COP.

Alteration of the blood-brain barrier produces leaky capillaries. Following capillary damage, both large and small molecules move across the blood-brain barrier such that it becomes impossible to establish a gradient for either across the capillary membrane. Under these circumstances, edema is primarily driven by changes in hydrostatic pressure, and neither changes in osmolality nor changes in COP have any effects.

In summary, if the blood-brain barrier is intact, total osmolality becomes the driving force for fluid movement. Since COP contributes only the equivalent of 1 mOsmol/kg, even enormous changes in COP will have little effect on fluid dynamics. In contrast, if the blood-brain barrier is damaged, neither an osmotic nor an oncotic gradient can be established in the area of the lesion, and edema formation is driven primarily by hydrostatic pressure. Osmotic changes may, however, alter water content in normal brain surrounding a lesion (13–17, 19, 25). Conceptually, one could postulate an area of partial capillary damage located in the periphery of a lesion, where fluid dynamics is similar to that seen peripherally. However, if such a zone exists, it was not identified among the sections of brain evaluated in our studies.

Clinical Recommendations

Translating laboratory observations into clinically applicable schemes requires care. In fact, the data presented do not conflict with conventional wisdom, which advocates fluid restriction in the preoperative period. An important clinical paper in the 1976 *Journal of Neurosurgery* by Shenkin et al. examined fluid management in neurosurgical patients (1). Patients with brain tumors were divided into three groups. One group received about 2 L/day of D5/0.45 NS. A second group received essentially the same fluid regimen plus dexamethasone. The third group, the fluid-restricted population, received approximately 1 L/day of D5/0.45 NS. The group receiving 2 L/day of D5/0.45 NS showed a progressive fall in plasma osmolality over 7 days. In contrast, the fluid-restricted group (1 L/day) remained isoosmolar over the postoperative period. This suggests that chronic fluid restriction may reduce brain water content (or prevent its increase) due to its osmotic effects.

However, the induction of general anesthesia to these fluid-restricted patients commonly results in hypotension. Under such circumstances, hypovolemia can be corrected using either crystalloids or colloids without adversely affecting brain water dynamics, as long as osmolality remains unchanged. Any commonly used intravascular replacement fluid will restore blood pressure to an acceptable range. The caveat is to select a fluid that will not reduce osmolality. If only 1 L of lactated Ringer's is infused, the resultant change in osmolality is unlikely to have any clinical effects. However, administration of large amounts of lactated Ringer's may lower osmolality sufficiently to increase brain water and hence raise intracranial pressure. In the uncommon circumstance requiring large fluid volumes, a change to either normal saline or a colloid compound in saline would be most appropriate.

Questions and Answers

Question: Do the various anesthetic agents affect brain water differently?

Answer: In a notable experiment, halothane, enflurane, isoflurane, and nitrous oxide–narcotic techniques were compared. Following establishment of a cryogenic brain lesion, animals were exposed to 6 hr of a selected anesthetic. The animals were killed 18 hr after termination of the anesthetic. The nitrous oxide–narcotic group showed less brain edema than the other groups, and the authors concluded that nitrous oxide–narcotic anesthesia was associated with less blood flow (more cerebral vasoconstriction), with lower intravascular hydrostatic pressures, and hence with less cerebral edema (26). However, a repeat of this study could not reproduce these findings (27). It may be that there is no clinically significant difference among the various modern techniques.

Question: Please explain the difference between fluid dynamics in the brain and in the lungs.

Answer: Lung parynchema is a very compliant tissue. It is difficult to generate an interstitial pressure in the lung because the interstitial space is expandable. The same thing occurs in peripheral tissues. If you measure interstitial pressure in subcutaneous tissue while infusing fluid, you will find that this peripheral compartment is also very compliant; the introduction of fluid into the space swells the tissue, but the pressure does not change very much. The brain is different. Unlike peripheral tissues, the brain is composed of cells that are tightly intertwined and contained within a rigid box. Consequently, the brain is very noncompliant, and measurements have confirmed this. Hence the normal brain resists edema formation. Some experimental data have shown that increases in interstitial compliance predispose to formation of brain edema; therefore, performance of a craniectomy increases the risk of brain edema (28, 29).

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The Role of Medication in Falls Among the Elderly in a Long-Term Care Facility

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Abstract

This case-control study examines the relationship between falls and drug use in elderly residents of a long-term care facility. The drug use and functional status of 57 first-time fallers were compared retrospectively with those of 90 residents who had never fallen. Fallers were taking significantly more drugs than controls. Hypnotic/anxiolytics and cardiac drugs carried a twofold increase in the risk of falling. Fallers were restrained less often, were more often ambulatory, and had been at the institution for a shorter time than controls. Previous studies have failed to use control groups or have selected controls by length of stay, possibly introducing bias into the results.

A large prospective study is needed to determine whether these results are generalizable to the elderly institutionalized population as a whole.

FALLS are the most common cause of both fatal and nonfatal injury in the elderly (1, 2). As one gets older, the risk of falling increases, as does the risk of injury from a fall (3).

In the United States, almost 200,000 hip fractures occur each year among people over 65 years old (4), and the majority of these fractures are associated with a fall. Hospital stays due to hip fractures are long and health care costs are high. The economic cost of hip fractures in the United States is approximately $7 billion per year (5).

Although only about 5%–10% of falls result in serious injury (4, 6, 7), the fall may cause severe emotional and psychological trauma. A fall may lead to loss of confidence, causing the elderly person to be less independent in activities of daily living.

In some studies, the incidence of falls in nursing homes is as high as 45% over two years (7). Nursing home residents tend to be older, more frail, and have more disabilities than elderly people who are living independently. Although this may contribute to the high incidence of falling, it does not present a complete explanation.

The factors that predispose the elderly person to a fall are not entirely clear. Falls usually have more than one cause (8), and medications have been implicated, although rigorous evidence is lacking (9). Studies have focused on the number of drugs a person is taking, as well as the specific types of drugs being taken. There are, however, conflicting reports on the relationship between drug use and falls.

The purpose of this study was to determine whether there is a relationship between drug use and first-time falling in nursing home residents. This study focuses on certain drugs implicated as risk factors for falling, including psychotropics, diuretics, antihypertensives, vasodilators, antibiotics, cardiac drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs).

The first author performed this study as part of a required third-year clerkship in Community Medicine at Mount Sinai School of Medicine (CUNY). He is now a resident, Department of Surgery, Thomas Jefferson School of Medicine, Philadelphia, PA.

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Methods

This study was conducted at The Jewish Home and Hospital for Aged (JHHA), a modern, 514-bed, long-term care facility in New York City. Of the 514 beds, 476 are designated as skilled nursing beds, the remainder as health-related care. JHHA is also the teaching nursing home of the Mount Sinai Medical Center and employs seven full-time physicians for medical management of patients. Safety features in the home include handrails, strong lighting, nonskid floors, and obstacle-free hallways. All rooms are accessible by elevator, which minimizes stair usage by the residents.

A case-control study design was employed. Cases were patients who experienced their first fall at JHHA during the 22-month period January 1987 through October 1988. This period was chosen to coincide with available pharmaceutical records.

For those who experienced multiple falls during this period, only the first fall was chosen for study. One rationale for choosing the first fall is that restraints are frequently ordered as a consequence of a fall (9). Additionally, a common practice at JHHA is the discontinuance of all unnecessary drugs after a fall. Mobility status also frequently changes as a result of a fall. For these reasons, the first fall was considered to be a more reliable and controlled event than subsequent events. Most studies have included all falls in a population over a period of time without controlling for multiple fallers. For this reason, there may have been a distortion of the actual drug use as a consequence of a patient's experiencing a previous fall.

A list of residents who had no history of falling was obtained. A table of random numbers was then used to select a control group. The charts of both groups were reviewed for age, sex, length of stay, ambulatory status, and restraint use. Medication exposure was obtained by using the computerized pharmacy files. Medications used on the day of the fall for case series were recorded. For the control group, the medication usage on a randomly selected index day during the 22-month period was recorded. The total number of drugs was noted, as were specific classes of drugs that may have contributed to a fall. These classes were antipsychotics, antidepressants, hypnotic/anxiolytics, diuretics, cardiac drugs (glycosides and antiarrhythmics), NSAIDs, vasodilators, and antihypertensives.

In calculating total number of drugs, the following criterion was used: all oral prescription medications were included, but external preparations not specifically used for transdermal absorption were not. In addition, over-the-counter (OTC) medications were included, since they may have an effect on the risk of falling (20). Vitamins and electrolyte supplements were not included.

Ambulatory status was extracted from the Activities of Daily Living (ADL) section of the Patient Review Instrument. This report is filled out semiannually on each patient for purposes of reimbursement. The ADL section contains four areas (mobility, transfer, eating, and toileting) which are evaluated in determining the amount of care a patient requires. Mobility is scored from 1 to 5; a score of 1 indicates that a patient is able to walk without supervision or human assistance. Scores of 2 or 3 represent decreasing independence, although the patient is considered ambulatory. Patients who cannot walk but can operate a wheelchair receive a score of 4. Finally, a score of 5 indicates that a patient must rely on another individual for movement. For purposes of this study, any patient who had a score of 1, 2, or 3 was deemed ambulatory; those who scored 4 or 5 were considered nonambulatory.

In order to analyze the data, continuous variables were compared between faller and control groups using Student's *t*-test. The chi-square test was used for analyses of all discrete variables. The odds ratio and its 95% confidence interval were calculated to assess the risk of falling for each drug class. Statistical significance was accepted at the $p < 0.05$ level.

Results

A total of 57 residents experienced a fall during the study period and 90 residents served as controls (Table 1). In the group of fallers, 45 of 57 were women, as were 78 of 90 in the control group. The mean age of the fallers was slightly higher than that of the controls; however, the difference was not statistically significant. Among the fallers, 29/57 were ambulatory, in contrast to only 30/90 in the controls. Restraints were used at least part of the day by a higher percentage of the controls (67.8%) than of the cases (10.5%) ($p < 0.001$).

The average length of stay was very different for the two groups (Table 1). The fallers had lived at The Jewish Home and Hospital for an average of 29.07 months before experiencing a fall, whereas the control group stayed for 43.42 months.

Fallers were taking an average of 1.05 more

TABLE 1

Demographic Characteristics and Functional Status of Fallers and Nonfallers

	Fallers ($n = 57$)	Controls ($n = 90$)	Significance
Sex (% male)	21.1	13.3	$\chi^2 = 1.52$, NS
Age ($\bar{x}$ ± SD)	87.17 ± 5.54	85.54 ± 7.01	$t = 0.23$, NS
Mobility (% ambulatory)	50.9	33.3	$\chi^2 = 4.40, p < 0.05$
Restraint (% restrained)	10.5	67.8	$\chi^2 = 46.10, p < 0.001$
Length of stay (months) ($\bar{x}$ ± SD)	29.07 ± 38.69	43.42 ± 41.45	$t = 13.40, p < 0.001$

drugs than the controls (5.37 for the fallers, 4.32 for the controls). Two classes of drugs, hypnotic/anxiolytics and cardiac drugs, were taken significantly more often by the fallers (Table 2). The risk of falling, as determined by odds ratio, was 2.54 times greater for residents taking either of these two drugs. In addition, it appeared that a greater number of fallers were taking antihypertensives, although this difference did not reach statistical significance. No relationship was found between falling and the use of antipsychotics, antidepressants, diuretics, NSAIDs, antibiotics, or vasodilators.

When controlling for ambulatory status (Table 3), both ambulatory and nonambulatory fallers were taking more drugs than similar controls. The odds ratio for the specific drug classes, cardiac and hypnotic/anxiolytic drugs, are all elevated but, because of the reduced sample size, do not reach statistical significance. It appears that by controlling for ambulatory status, the magnitude of the drug-related risk of falling is only slightly affected (the odds ratio range is 1.91–4.46), although the degree of statistical confidence is reduced.

Discussion

The results show a significant difference in functional status between fallers and controls. Fallers, in this study, tend to be older and more ambulatory and less frequently restrained than controls.

Older Age. There is general agreement in the literature that older age is a risk factor for falling (7, 10–12), although the risk may not be so much old age as the increasing illness and frailty that accompany aging.

Degree of Mobility. In 1981, Campbell et al found that in an ambulatory community population, fallers tend to have more impairment of mobility (10). If this is true, the greatest risk of falling would exist among the elderly who have impaired mobility but can still walk (that is, those who are most unsteady on their feet).

Restraints. Although the use of restraints appears protective in this study, restraints may cause physical and emotional harm, so that the "benefit" of protection from falling might be offset (11). Restraining a patient may contribute to a feeling of helplessness and loss of confidence, in

TABLE 2

Drug Use (%) Among Fallers and Nonfallers

Drug	Fallers	Nonfallers	Odds ratio	95% Confidence interval
Antipsychotics	17.5	16.7	1.06	0.40, 2.78
Antidepressants	19.3	11.1	1.91	0.69, 5.33
Hypnotics/anxiolytics	28.1	13.3	1.54	1.02, 6.38
Diuretics	28.1	37.8	0.64	0.29, 1.40
Cardiac	28.1	13.3	2.54	1.02, 6.38
Antihypertensives	12.3	6.7	1.96	0.55, 7.06
NSAIDs	19.3	13.3	1.55	0.58, 4.15
Antibiotics	12.3	11.1	1.12	0.36, 3.46
Vasodilators	24.6	22.2	1.14	0.48, 2.67
Number of drugs (mean ± SD)	5.37 ± 2.6	4.32 ± 2.3	$t = 3.96, p < 0.001$	

TABLE 3
Drug Use (%) Among Fallers and Nonfallers by Ambulation Status

Drug	Fallers	Nonfallers	Odds ratio	95% Confidence interval
Ambulatory	N = 29	N = 30		
Hypnotics/anxiolytics	27.6	16.7	1.91	.46, 8.06
Cardiac	24.1	6.7	4.46	.73, 21.68
No. of drugs (mean ± SD)	5.6 ± 2.9	4.1 ± 2.5	t = 3.53, $p < .001$	
Nonambulatory	N = 28	N = 60		
Hypnotics/anxiolytics	28.6	11.7	3.03	.85, 10.93
Cardiac	32.1	16.7	2.37	.74, 7.62
No. of drugs (mean ± SD)	5.1 ± 2.5	4.4 ± 2.3	t = 1.94, $p < .05$	

addition to the restriction in the quality of life (13, 14). Restraints may also lead to bed sores, muscular atrophy, and decreased circulation to the extremities (13). Although these are serious problems, restraints may be the best preventive measure currently available in populations of recurrent fallers.

Length of Institutionalization. In this study the average length of stay was approximately 14 months longer for the controls than for the fallers. This indicates that the question is not simply length of stay, but rather what other specific factors may increase the likelihood of falling. In a study by Granek et al, controls were selected solely on the basis of length of stay (14). This study found a higher risk of falling among residents taking antidepressants, sedative/hypnotics, vasodilators, NSAIDs, and tranquilizers. The researchers also determined that falls are more closely associated with specific drugs than with the medical conditions for which the drugs are prescribed. These results, however, may be skewed because of the way the control group was selected.

Number of Medications. The central purpose of the study we performed was to determine whether there is an association between drug use and falling. The results showed that fallers were taking more medications than were controls. This finding supports that of other researchers (14–16). There are two reasonable explanations for this finding. One is that the overall use of medications is associated with an increased risk of falling. The other is that an increased number of medications indicates a greater degree of illness, and the illness is the key factor in causing a fall. To distinguish between the two, it would be necessary to know the degree of illness of each patient.

Degree of Debilitation. For this study, ambulatory status was chosen as a crude measurement of degree of debilitation. In general, a patient who can walk is probably less ill than one who is bed-bound. When controlling for ambulatory status, more drugs were still found to be taken by the fallers. This may mean, then, that the risk of falling is associated with drug use after the degree of illness is taken into account. In looking at drugs and diagnoses in relation to falling in nursing home patients, Granek et al in 1987 also found that falling was associated more with drug use than with degree of illness (14).

Classes of Drugs. Examination of the relationship between falls and different classes of drugs resulted in some interesting findings. Hypnotix/anxiolytics were used significantly more often by fallers than by controls. This finding supports that found by other researchers (14, 17, 18). This class of drugs produce sedation and lethargy and may also produce confusion, ataxia, and dizziness (18, 19). In addition, benzodiazepines, the most common type of hypnotic/anxiolytic, may cause orthostatic hypotension (20). For this reason, it is easy to envision a fall occurring in a person who is taking a hypnotic/anxiolytic. In this study, cardiac drugs (glycosides and antiarrhythmics) were also associated with falling. Wells and associates similarly noticed an increased number of cardiac drugs among fallers, although the results were not significant (16).

Cardiac Drugs and Hypnotics/Anxiolytics. Wells et al (16) found the diagnosis of congestive heart failure three times more often in fallers than in controls. They concluded that congestive heart failure was a risk factor for falling. However, the use of digoxin was not recorded. This study suggests that cardiovascular disease requiring digoxin or cardiac drugs in general may be a risk factor for falling; congestive heart failure is the most common diagnosis in those using cardiac drugs. The mechanisms by which cardiac drugs could contribute to falls are many, cardiac syncope and arrhythmias being the most well known (12).

When controlling for ambulatory status, the risk ratios for cardiac and hypnotic/anxiolytic drug exposure remained elevated in both ambulators and nonambulators but did not reach statistical significance. This is undoubtedly due to consequences of reduced sample size when splitting the sample into the two subsets. It therefore appears that ambulatory status does not have an effect on the relationship between falls and the use of these drugs.

Future studies that control more rigorously for degree of debilitation would be useful to determine the relationship between falls, diseases, and drugs.

For those residents taking hypnotic/anxiolytics or cardiac drugs, the risk of falling was over two and one-half times greater than for those who were not taking these drugs. Caution should be used when prescribing these drugs, and alternate methods of treatment should be considered when available. Because the pharmacokinetics of drugs in the elderly is not the same as in the young (21), blood levels of these drugs should be monitored to avoid toxic levels, which may predispose a person to fall.

The classifications used in this study are broad. Because of the small size of this study, the relationship between falling and use of individual drugs (diazepam, digoxin) could not be assessed accurately.

This study also found that the chance of falling was not proportional to the length of stay. In fact, falls on the average occurred earlier rather than later. This could be due to any one of a number of risk factors, including the resident's lack of familiarity with the new environment of the nursing home.

There are other risk factors that have not been studied adequately. A large prospective study is needed to assess the relationship between falls and such factors as drug dosage, duration of drug use, mental status, and number of chronic diseases. The literature in recent years shows that falls are not an inevitable aspect of aging (22), as had been assumed in the past (23). Clearly, if preventive measures are taken, the enormous number of falls that occur each year could be reduced, thus improving the quality of life in the elderly.

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Efficacy of Long-Term Fluoxetine Treatment of Obsessive-Compulsive Disorder

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Abstract

Ten outpatients meeting DSM-III-R criteria for obsessive-compulsive disorder completed a 32-week, open-label study with fluoxetine, a selective serotonin reuptake blocker. The patients were evaluated every four weeks for obsessive-compulsive symptomatology, anxiety, and depression. Significant improvement of obsessive-compulsive and anxiety measures were observed after four weeks, with maximal improvement at eight weeks. Depressed and nondepressed patients showed similar rates of improvement in obsessive-compulsive symptomatology. Overall, fluoxetine was tolerated well by all patients, and no serious side effects were observed. This study suggests that fluoxetine is an effective and safe treatment for obsessive-compulsive disorder, both for short-term alleviation and for long-term maintenance.

THE OBSERVATION that clomipramine (CMI) improved obsessive and compulsive symptoms in depressed patients (1) prompted a new search for effective agents for obsessive-compulsive disorder (OCD), one of the most treatment-resistant psychiatric illnesses (2). Further studies confirmed that CMI, a serotonin (5-HT) reuptake inhibitor (3), was efficacious in reducing obsessive-compulsive symptoms, in comparison with both placebo and other tricyclic antidepressants (4–7). These findings led to formulation of the serotonin hypothesis of OCD (8, 9) and to development of other serotonergic agents in the treatment of this disorder (10–16).

Fluoxetine is a novel bicyclic antidepressant (17, 18). It is a highly selective 5-HT reuptake inhibitor both in vitro and in vivo, with negligible effects on other neurotransmitter systems (17).

In several recent studies (12–15), fluoxetine was found to be helpful in obsessive-compulsive patients, reducing both compulsions and obsessions. Three of these four studies were short term (8–10 weeks). We report the results of an eight-month pilot project assessing the long-term efficacy and safety of fluoxetine in the treatment of OCD.

Methods

Patient Selection. Ten patients (six male and four female) meeting DSM-III-R criteria for OCD were selected from patients referred to the Beth Israel Medical Center Psychiatric Clinic. Only seriously ill patients were chosen, that is, those whose illness was severe enough to interfere significantly with their daily activities, including work and social life. Patients with other anxiety disorders, psychotic illness, organic mental syndromes, substance abuse, or significant medical illness were excluded from this study. Patients with depression ($n = 3$) were accepted.

The duration of OCD among these patients varied from 8 to 20 years (mean: 14.3 years). All patients in this sample had in the past been

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given extended trials of various medications, including neuroleptics, antianxiety agents, and antidepressants, which were largely ineffective. One notable exception was clomipramine. All four patients who had received this agent reported significant improvement of their obsessive-compulsive symptoms while taking it.

Study Design. This was an open-label, noncomparative study, conducted for 32 weeks. Prior to entering the study all patients gave informed consent and had a physical examination, routine laboratory tests, and an electrocardiogram. All psychotropic medication except benzodiazepines (given for anxiety) was discontinued two weeks prior to treatment with fluoxetine. Eight of ten patients remained on low-dose benzodiazepine treatment on an as-needed basis throughout the study. Five patients received 0.5 mg of alprazolam; two patients received 1 mg of lorazepam; and one patient received 5 mg of diazepam. The patients were evaluated every four weeks. On each visit their blood pressure, pulse, and weight were recorded, and the routine laboratory tests were repeated.

Fluoxetine was provided in 20-mg capsules. Treatment was begun during the first visit in the following manner: day 1, 20 mg; day 2 and 3, 40 mg; day 4–7, 60 mg; day 8, 80 mg. Throughout the study period, the dose was adjusted individually, based on patient tolerance and clinical response. Fluoxetine was given in the morning during the first few days and then in two divided doses, in the morning and early afternoon.

Assessment by Physician Ratings. Assessment of the patients' clinical status was performed before treatment and then every four weeks in an interview with a research psychiatrist. The following measures were used by the raters: Hamilton Rating Scale for Depression (HAM-D) (19); Hamilton Rating Scale for Anxiety (HAM-A) (20); a seven-point severity scale (OC-S), to assess the severity of the obsessive-compulsive symptomatology (1 rating as normal and 7 as extremely severe); and a Global Improvement Scale (GIS-T) to assess the symptomatic improvement (a 7-point scale on which 1 rated as very much improved and 7 as very much worse).

Assessment by Patient Self-Report. The patients completed the Symptom Check List (SCL-58) (21), including a nine-item obsessive-compulsive inventory (SCL-OC), which was scored and analyzed separately. In addition, the patients completed a Global Improvement Scale (GIS-P) to rate their impression of the change in their obsessions and compulsions from the point at which fluoxetine was initiated (a 7-point scale on which 1 rated very much better and 7 as very much worse).

Assessment by Statistical Analyses. For each of the various outcome measures, a one-way (over the nine assessment points) repeated-measures multivariate analysis of variance (MANOVA), using a multiple profile procedure, was initially conducted. If the results of this overall MANOVA reached statistical significance (alpha level of .05), then various individual univariate F-tests were performed to evaluate the differences among means. These F-tests used pooled error terms derived from the relevant original MANOVAs. This overall procedure is conservative and adequately controls for family-wise error rates due to the large number of individual contrasts conducted.

Results

All 10 patients who were accepted completed the study (Table).

Physician Ratings. The initial analyses indicated significant changes over time in the following four therapist-related measures: HAM-D, HAM-A, MANOVA $F(8,2) = 12.99$, $p < .003$; MANOVA $F(8,2) = 6.49$, $p < .02$; OCD severity scale, MANOVA $F(8,2) = 5.03$, $p < .02$; and GIS-T, MANOVA $F(7,3) = 9.21$, $p < .01$. Individual contrasts further indicated that, at the end of the first four weeks, only the depression scores were significantly lower compared to pretreatment assessment, $F(1,9) = 17.89$, $p < .002$. Differences between pretreatment and four-week status on the other two measures were not significant (note that the GIT measure was first obtained at the four-week assessment point). However, by eight weeks, mean scores on the HAM-A, OCD severity and GIS-T scales were significantly lower than pretreatment scores ($F[1,9] = 12.80$, $p < .007$; $F[1,9] = 5.44$, $p < .03$; $F[1,8] = 8.19$, $p < .02$, respectively).

At the end of 12 weeks, depression scores showed an additional significant decrease, as compared to the week 4 evaluation, $F(1.9) = 5.44$, $p < .04$. No additional significant changes were noted for the other three measures at this assessment point. Results of further individual contrasts revealed no significant additional decreases or increases in mean scores of these four measures throughout the remaining assessment points, which suggests stable maintenance of improvement after 8 weeks of treatment.

Patient Self-Report Measures. The three patient self-report measures paralleled the ratings by therapists. Specifically, initial MANOVA

TABLE 1

Eight-Month Assessment of Fluoxetine in Treatment of 10 Patients with Obsessive-Compulsive Disorder, Means and SD

	Physician ratings				Patient self-report		
Assessment period	HAM-D	HAM-A	OCD severity	GIS-T	GIS-P	SCL-58	SCL-OC
Pretreatment	17.10	7.70	6.40	—	—	136.00	26.30
	(5.92)	(2.67)	(0.52)	—	—	(20.82)	(4.19)
Week 4	9.80	5.89	6.10	2.80	3.10	115.70	22.10
	(4.66)	(2.26)	(0.88)	(1.14)	(0.74)	(19.56)	(4.75)
Week 8	7.70	4.30	5.40	1.90	2.30	109.56	20.33
	(3.83)	(2.26)	(0.97)	(0.74)	(0.95)	(24.28)	(4.15)
Week 12	6.80	4.00	5.60	1.90	2.20	109.86	20.90
	(2.70)	(1.97)	(1.08)	(0.74)	(0.82)	(28.41)	(5.89)
Week 16	6.00	3.40	5.60	1.70	1.70	102.80	19.00
	(3.89)	(1.65)	(1.08)	(0.68)	(0.82)	(28.41)	(4.14)
Week 20	6.50	4.00	5.60	1.60	2.00	102.80	19.30
	(3.21)	(2.45)	(1.08)	(0.69)	(0.82)	(27.70)	(4.67)
Week 24	5.90	3.50	5.20	1.50	1.90	107.80	20.60
	(3.28)	(2.32)	(1.48)	(0.71)	(0.74)	(38.08)	(6.42)
Week 28	6.80	3.80	5.40	1.80	1.80	108.10	21.00
	(3.71)	(2.35)	(1.08)	(0.63)	(0.63)	(29.53)	(6.09)
Week 32	6.40	4.20	4.70	1.50	1.80	104.10	20.60
	(3.73)	(2.62)	(1.95)	(0.71)	(0.79)	(27.29)	(5.99)

HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; OCD severity, physician rating of obsessive-compulsive severity; GIS-T, Global Improvement Scale-Physician; GIS-P, Global Improvement Scale-Patient; SCL-58, Symptom Checklist-58; SCL-OC, Obsessive-Compulsive Inventory of the SCL-58 (9 items).

findings indicated significant overall effects for the SCL-58 MANOVA $F(8,2) = 27.08$, $p < .001$; the obsessive-compulsive inventory (SCL-OC) of the SCL-58, MANOVA $F(2,8) = 10.98$, $p = < .007$; and the GIS-P, MANOVA $F(7,3) = 12.09$, $p < .01$. By week 4, mean SCL-58 and SCL-OC scores were found to be significantly lower than pretreatment, $F(1,9) = 20.39$, $p < .002$; $F(1,9) = 15.36$, $p < .004$, respectively. Differences between week 4 and week 8 GIS-P scores were also significant, $F(1,8) = 16.00$, $p < .003$. No further significant additional changes, either increases or decreases in mean scores, were noted after 32 weeks for any of these three measures, again suggesting a stable maintenance profile. As with clinician-rated measures, improvements in symptomatology accrued by week 8 remained stable throughout the remainder of the study.

Relation of Depressive Severity to Effectiveness of Treatment. To determine whether severity of pretreatment depression moderates the effects of fluoxetine on OCD symptomatology, a second set of analyses was conducted. Essentially, the 10 patients were divided into two groups as a function of their pretreatment HAM-D scores. Subjects receiving a HAM-D score of 20 or greater ($n = 3$) were assigned to a "depressed" group, subjects with HAM-D scores of less than 20 ($n = 7$) to a "nondepressed" group. A series of 2 (group) × 9 (assessment period) repeated-measures MANOVAs were conducted to determine whether group differences emerged in changes in overall symptomatology. According to this design, the presence of significant interaction effects would suggest differential response rates to the effects of fluoxetine.

Results of these analyses indicated no significant interaction effects in any of the measures, and no significant main effects concerning differences in group assignment. As would be expected, the main effect representing the different assessment periods was found to be highly significant for all outcome measures (see results above).

This pattern of findings suggests that pretreatment depression level did not moderate the effects of fluoxetine on OCD symptoms, as measured by both physician ratings and patient self-ratings. In other words, regardless of one's level of depression prior to fluoxetine treatment, the effects engendered by fluoxetine use were found to be similar.

Drug Dosage. The dose of fluoxetine was increased from 20 mg daily to a maximum of 80 mg daily at the eighth day. Nine patients tolerated this regimen and were maintained on the maximum dose throughout the study. One patient developed marked restlessness and irritability at week 4 while on 80 mg daily. This patient's medication was decreased gradually to 20 mg daily, at which point all adverse symptoms disappeared, and she was able to complete the study successfully. This suggests that some patients may not require 80 mg/day or that the drug dose can be reduced to a lower maintenance level once significant symptom reduction occurs.

Side Effects. The incidence of side effects was remarkably low. Two patients reported restlessness and irritability. In one it was mild and related to premenstrual tension; in the other it was moderate and necessitated a reduction of medication. A third patient developed mild, transient drowsiness, which lasted a few days. Another patient complained of disturbing dyspepsia, which responded to antacids. In addition, in two patients there was a slight transient elevation of liver function test results (SGOT, LDH, and alkaline phosphatase).

Weight. Weight changes were nonuniform. After 32 weeks we found that four patients lost weight (range 2–26 lb), four others gained weight (range 4–23 lb), and in two patients the weight remained unchanged. Recordings of weights on each visit showed wide variation and inconsistency, both in the same patient and in the group as a whole. Interestingly, one of the patients whose weight did not change overall had periods of bulimic behavior before and during the study. After 8 weeks these episodes completely disappeared.

Discussion

This study documents the results of a long-term investigation of fluoxetine in the treatment of obsessive-compulsive disorder. Our findings suggest that fluoxetine was efficacious in significantly reducing obsessions and compulsions in all participating patients ($n = 10$), and that the therapeutic effect was maintained as long as the medication was administered. There was a concomitant significant improvement in the depression and anxiety scores, which remained stable once the maximum response was achieved. The obsessive compulsive (SLC-OC) and the anxiety (HAM-A) measures showed significant and maximum improvement after 8 weeks and then remained stable throughout the 32 weeks of the study. In the depression measure (HAM-D), significant improvement was recorded after 4 weeks, reaching a maximum change after 12 weeks and remaining stable for the rest of the study period.

These findings correlated well with the patients' and the physicians' ratings of the global improvement in obsessive-compulsive symptomatology (GIS-P and GIS-T, respectively), which also reached their maximum after 8 weeks. Unlike a report in another study (13), we found that patients' and physicians' ratings of improvement were similar, although patients tended to rate themselves higher on symptom measures.

Since this was a pilot study, a randomized, double-blind design was not employed. However, two recent reports indicate there is no significant placebo response in OCD (22, 23). If OCD patients have concomitant depression, placebo may alleviate depressive symptoms, but not OCD itself.

Finally, the fact that patients were given benzodiazepines on an occasional as-needed basis has been shown to have little or no effect in the treatment of OCD. The only exception to this may be clonazepam (24), which was not used in our study.

Conclusion

Our data suggest that a trial of 8 weeks should be given when treating OCD with fluoxetine, since a favorable response may not occur until then. If no change is noted after 8 weeks, the chances of a later response are small. With regard to fluoxetine's antidepressant effect, it seems that a longer period of 12 weeks might be necessary for a maximum response to occur.

Unlike a previous report (12), we found that the pretreatment depression score (HAM-D) did not correlate with the rate of change in the obsessive-compulsive score (SCL-OC); that is, a similar rate of improvement in obsessive-compulsive symptomatology was found in all patients, regardless of the severity of their pretreatment depression scores (HAM-D), even when those were very low (<10). This finding may indicate that the antidepressant and the anti-obsessive-compulsive effects of fluoxetine coincide, but are independent of each other.

We found fluoxetine to be a safe drug. Throughout the eight months of the study, there were no significant adverse effects or dropouts. This novel agent appears to be a rational choice in the initial treatment of OCD.

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Effects of Intravenous Ethanol on Basal Bile-Pancreatic Secretion in Nonalcoholic and Alcohol-Fed Rats

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Abstract

In nonalcoholic (NA) and alcohol-fed rats (AF), intravenous-ethanol-induced percentage changes in bile-pancreatic-secretion (BPS) were evaluated, with and without gastric juice diversion (GJD) and with and without BPS duodenal recirculation (DR). Even with GJD, ethanol elicited a slight increase in BPS. These changes were greater in AF animals even when performed without GJD. When intravenous ethanol was given under conditions of GJD and DR, there were marked differences between the NA and AF animals in the ethanol-elicited post-plateau percentage changes of BPS. NA animals evidenced no significant difference from controls. But in the AF rats, ethanol triggered a marked and significant increase of flow, protein concentration, and output that became progressively greater in successive collection periods. It is postulated that without DR, and the resulting lack of negative duodeno-pancreatic reflexes (DPR), there occurs a change in reactivity to intravenous ethanol of the hypothalamic-bulbar nuclei (HBN) and in the mechanisms that modulate the flow of cholinergic impulses through the intrapancreatic ganglia (IPG). The postulated consequence is predominance (slight in NA rats receiving intravenous ethanol, greater in AF rats) in discharge of positive impulses from HBN and flowing unimpeded through the IPG to the "pancreon" units. In the NA animal with DR, ethanol may enhance BPS values, but in the AF rats, impairment of the negative DPR elicited by chronic alcohol intoxication might, after an acute intravenous ethanol injection, favor the discharge of positive impulses from the HBN flowing unimpeded through the IPG. In the AF rats also, ethanol would activate the nonnicotinic receptors of the neurons of the "antral," "duodenal," and "celiac" autonomic brains. Together these factors may contribute to enhanced intrapancreatic cholinergic tone, postulated to be responsible for the increased leaking of albumin in the BPS observed in the present study.

ON the basis of a series of experiments performed in rats, dogs, and humans (1–35), we have developed the concept that ethanol intoxication, either acute or chronic, in nonalcoholic (NA) or alcohol-fed (AF) subjects, acts on the "pancreon" units (36) by an indirect mechanism via the autonomic nervous system. During the nonalcoholic stage, acute administration of ethanol might trigger the discharge of vagal impulses, both inhibitory and excitatory, primarily from the central nervous system (hypothalamic-brain-stem nuclei). In the nonalcoholic period, the inhibition appears to predominate. In the alcohol-fed stage, the inhibitory component of pancreatic innervation might progressively decrease so that the excitatory component becomes evident (32, 33, 37, 38).

In the alcohol-fed stage there is enhanced choline-acetylase activity in the pancreas that

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can be demonstrated by histochemical (25) and biochemical (29) methods.

Because the reports on the effects of intravenous ethanol on basal pancreatic secretion (39, 40) are contradictory, we decided to study the phenomena using a bile-pancreatic fistula model (28, 41) with a high index of reproducibility. Tests were performed in nonalcoholic (NA) and alcohol-fed (AF) rats. In both groups, the ethanol-elicited changes were assessed with and without gastric juice diversion (GJD). Studies were also designed to assess whether duodenal recirculation (DR) with bile-pancreatic secretion (BPS) influences the "pancreon" secretory response to acute intravenous ethanol.

Materials and Methods

Experiments were performed on 103 male Wistar rats in which bile-pancreatic fistulas were created (28, 41) while the animals were under ether anesthesia.

A metal cannula with a flange secured to the stomach wall with a purse-string was inserted in the rumen segment and brought to the left flank of the abdomen. Finally, plastic tubing was inserted in the right external jugular vein. A Silastic catheter was connected to the plastic tubing and was brought to the neck. Through it either an isotonic saline solution or ethanol diluted in isotonic sodium chloride solution was infused at the end of the "plateau" stage.

All surgical procedures were carried out during the morning hours; the animals were not deprived of food beforehand. Rats were tested during the first two days following surgery. Tests were performed in conscious animals placed in Bollman restricting cages (42). After the functional evaluation, the two catheters in the neck were connected to each other to allow recirculation of bile-pancreatic juice into the gut, and animals were transferred to their cages for standard maintenance, without any movement restriction, in fasting condition and drinking water ad libitum. During this two-day period the bile-pancreatic juice flow rate is regular and reproducible.

Testing was always done during the morning hours, at room temperature. The basal bile-pancreatic juice was collected in small calibrated tubes immersed in crushed ice. Before the collection periods began, the gastric cannula was opened to divert the gastric juice to the exterior. This step was omitted in those tests in which the effects of intravenous ethanol was evaluated under conditions of nondiverted gastric juice. The collection periods were 30 min each. The average values of the second and third periods were designated the "plateau." The following biochemical assays were made:

- Flow (ml in 30 min), measured with a precision of 0.1 ml.
- Bicarbonate concentration (HCO_3^- in mEq/1), determined by the titrimetric method described by Lehmann et al (43).
- Bicarbonate output, calculated and expressed as μEq/30 min.
- Protein concentration, measured by the method described by Gornall et al (44).
- Protein output, expressed as mg/30 min.
- Lipase concentration, determined by the method of Lehmann et al (45).
- Lipase output, expressed as Lehmann units/30 min.

In addition, the concentration of albumin in the three pooled samples of BPS was determined (46) before and after ethanol or saline infusion.

Several groups of rats were studied:

- **Normal, nonalcoholic**
  - with GJD
  - without GJD
  - without DR, without GJD
- **Alcohol-fed**

Animals were alcohol fed for three months, during which time they were allowed to drink only a solution of ethyl alcohol according to the following schedule: first week, 5% solution (v/v); the next two weeks, 10% (v/v); the following week, 15% (v/v); the fifth week, alcohol dose was increased to 25% (v/v). On the 90th day, the animals received a solution of 30% (v/v) alcohol.

In general, this group of rats weighed less than the nonalcohol-fed animals.

The mean and standard error of the mean of the results were calculated. Differences were expressed as a percentage change from the initial plateau value. The significance of the percentage change was evaluated using Student's t test for nonpaired values. P values less than 5% ($p < 0.05$) were interpreted as significant (47). The differences between the various test groups studied were also calculated as percentage changes. Significance was determined using the t test for nonpaired values (47).

Results

Control Series. In the first series, the spontaneous post-plateau percentage changes of BPS under conditions of GJD but without DR revealed a slight and progressive decline. This type of response is virtually unaltered by intravenous injection of saline (Fig. 1).

The second series (Fig. 2), of rats fed alcohol for six months, showed that the spontaneous post-plateau variations of BPS without DR and GJD do not differ from the responses observed in NA animals.

Studies in NA animals and in AF animals (Fig. 3), under conditions of DR and GJD, revealed no significant changes in BPS compared to the control plateau.

Experimental Series. In the first series, the comparison between intravenous saline and intravenous ethanol with GJD and without DR disclosed a slight but significant effect of ethanol and saline (Fig. 1).

In the second series, evaluation in NA animals with and without DR and with and without diversion of gastric juice, the presence of gastric juice provides a significant excitatory effect on BPS (Fig. 2). A lesser effect is seen with gastric juice diversion.

In the third series, a repeat investigation of the second series but performed on animals fed alcohol for 3 months (Fig. 4), the result was that—as in the NA rats—even with diversion of gastric juice, intravenous ethanol elicits a significant effect on BPS. It is striking that increase in protein concentration and output is sustained more when the gastric cannula is open than when it is closed.

A fourth series, comparison of ethanol-evoked effects on the BPS plateau values with DR and GJD in NA and AF animals, disclosed marked and significant differences of BPS. Indeed, intravenous ethanol in AF rats triggered a slight, significant increase in flow (Fig. 5) and a highly significant rise of protein concentration and output. In contrast, in NA rats, the pattern of BPS changes following intravenous ethanol does not differ from that of the control series.

BPS Albumin Concentration Changes Induced by Isotonic Saline and Ethanol. Analysis carried out in the first series of animals of the experimental group, i.e. pre- and post-intravenous injection of either isotonic saline or ethanol, revealed total protein and albumin in the BPS of the ethanol-treated group significantly higher than in animals treated with isotonic saline (Fig. 6, Table).

Discussion

Intravenous ethanol administration in rats without DR elicits an excitatory effect on BPS even when gastric juice is prevented from enter-

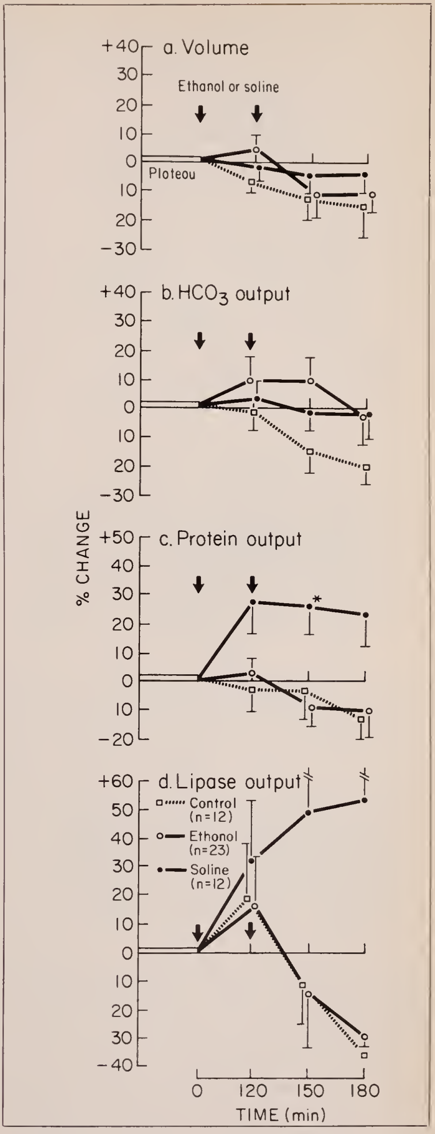

Fig. 1. First experimental series: Ethanol-induced changes in nonalcoholic (NA) rats without duodenal recirculation (DR) with gastric juice diversion (GJD): volume, HCO_3 output, protein output, lipase output; $*p < 0.05$.

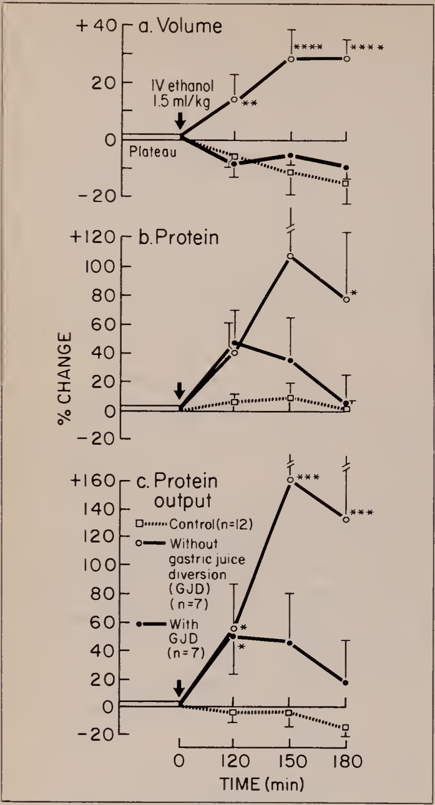

Fig. 2. Second experiment series: changes induced by intravenous (IV) ethanol on nonalcoholic (NA) rats with and without duodenal recirculation (DR) and gastric juice diversion (GJD): volume, protein, protein output; *vs control, $p < 0.05$; **vs control, $p < 0.025$; ***vs control, $p < 0.01$; ****vs control, $p < 0.001$.

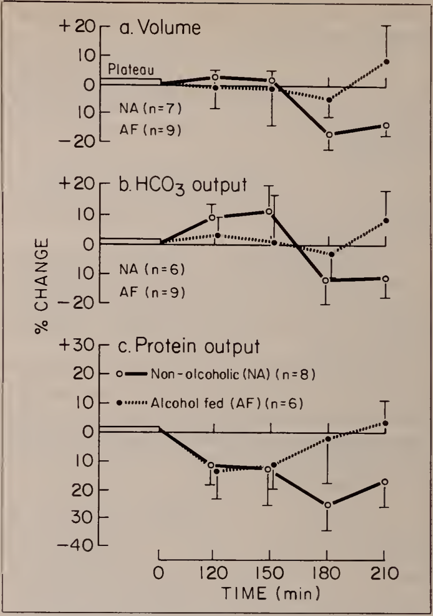

Fig. 3. Control series. Rate of flow of bile-pancreatic secretion (BPS). Post-plateau spontaneous BPS percentage changes in nonalcoholic (NA) and alcohol-fed (AF) rats with duodenal recirculation (DR) and gastric juice diversion (GJD): percentage changes in rate of flow, percentage changes in bicarbonate concentration, percentage changes in protein output.

ing the duodenum. This is observed in both NA and AF animals, although the stimulatory influence is more marked in the chronically alcoholic animals.

In studies in rats with DR, intravenous ethanol evokes a different response in NA and AF animals. Indeed, in NA rats, intravenous ethanol does not induce significant change from controls of flow, protein concentration, or protein output. In contrast, in the alcohol-pretreated rats, intravenous ethanol triggers an increase in flow rate as well as a marked augmentation of protein concentration and output.

The overall results of these investigations are concordant with our previous findings and support our hypothesis (1–35) that an acute intravenous ethanol infusion stimulates excitatory impulses to the pancreas from the central nervous system (hypothalamic-bulbar centers). This happens in both NA and AF animals, although the change is much more marked in the latter. In nonalcoholic humans, intravenous ethanol inhibits its pancreatic secretion, whereas in the nonalcoholic rat, ethanol does not have that inhibitory effect. The inhibition in humans we have attributed to an activation of vagal inhibitory fibers (48–50). Thus, in the rodent, intravenous ethanol evokes from the very beginning an excitatory influence, although it is evident that this hypersecretory protein effect is more marked in the chronically alcoholic animal.

Korsten et al (40) also observed the effects of intravenous ethanol on rat basal pancreatic secretion. They argue that a lack of inhibitory ef-

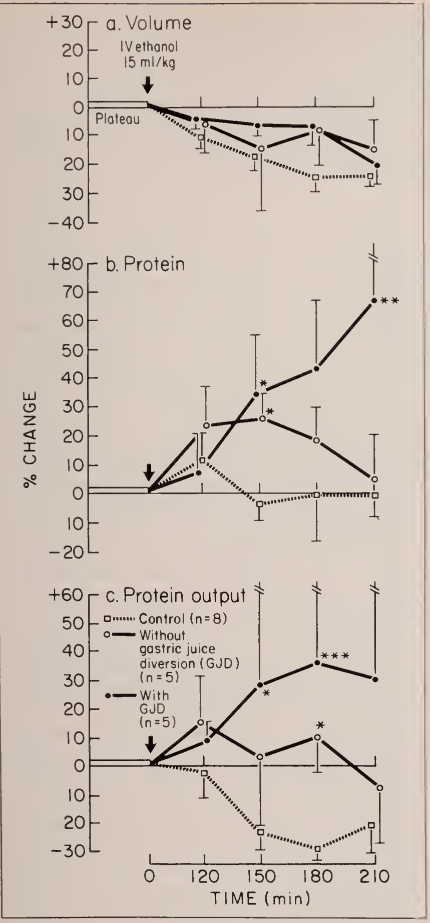

Fig. 4. Third experimental series: Effects of ethanol infusion on alcohol-fed (AF) rats without duodenal recirculation (DR), with and without gastric juice diversion (GJD): *vs control, $p < 0.05$; **vs control, $p < 0.025$; ***vs control, $p < 0.01$.

fects on basal pancreatic secretion militates against our hypothesis that ethanol may act indirectly on the pancreas through mediation of the autonomic nervous system. We thereby must clarify our idea in the sense that we equate vagal inhibitory fibers to what is known today as the inhibitory peptidergic pathway. This is represented mainly by pancreatic polypeptides such as the cholinergic-dependent or other peptides like enkephalins, somatostatin, substance P. That the inhibitory peptidergic pathway might be the one predominantly activated by intravenous ethanol in the nonalcoholic stage can be inferred from the experiments performed in humans (1) and dogs (3, 14). However, the ethanol-induced activation of this inhibitory pathway might become less as the alcohol-fed stage advances (5, 6, 19, 21, 22). It is noted that during long-term alcohol feeding, intravenous ethanol progressively induces an excitatory response. Since atropine pretreatment prevents this response (11), the phenomenon is presumably a consequence of the discharge of cholinergic impulses. Furthermore, on the basis of its persistence after truncal vagotomy (4), it appears that ethanol activates the peripheral cholinergic neurons releasing acetylcholine at the nerve endings and, consequently, enhances intrapancreatic cholinergic tone (6, 9, 11, 12, 16, 20, 23–25, 26, 29, 30–34).

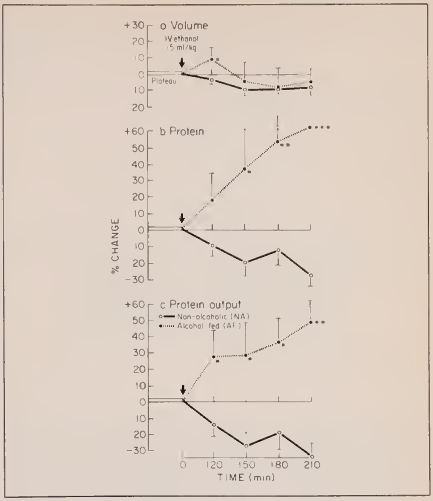

Fig. 5. Fourth experimental series: Rate of flow of bile-pancreatic secretion (BPS). Tests performed on 11 nonalcoholic and 6 alcohol-fed rats with duodenal recirculation (DR) and gastric juice diversion (GJD): ethanol-induced percentage changes in "plateau" levels in 11 NA and 6 AF rats; protein concentration of BPS; protein output of BPS. *$p < 0.05$; **$p < 0.025$; ***$p < 0.01$.

In the rat (29, 30), we have also shown that this phenomenon is not restricted to the pancreatic gland. We have recently demonstrated that during the alcohol-fed stage, ethanol-evoked positive cholinergic impulses might originate not only in the central nervous system (hypothalam-

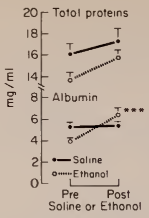

Fig. 6. Changes induced by either intravenous isotonic sodium chloride or ethanol (2.0 mL/kg) in concentration of total protein and albumin of BPS. Comparison of values observed in pool of pre- and post-plateau collection periods; $^{***}p < 0.01$.

ic-bulbar centers) but also in the "intermediate autonomic brains," that is, the "antral," "duodenal," and "celiac" brains, as well as in the intrapancreatic ganglia (32, 33). Ethanol, like scorpion venom (51), is able to impinge on cholinergic neurons, upon nonnicotinic receptors releasing acetylcholine at the postganglionic ending. This peripheral effect of ethanol would be accentuated during the alcohol-fed stage due to some sort of vagal decentralization triggered by an ethanol-induced lesion of the vagal nerves (52). Ethanol could also be implicated in the subsensitivity of the ganglionic nicotinic receptors. This would be a consequence of ethanol-induced nervous impulses. As a result there would be enhancement of the nonnicotinic pathways, activated by CCK and ethanol itself.

In support of our hypothesis of an ethanol-evoked high intrapancreatic cholinergic tone is the diminished acetylcholinesterase activity of the nerve endings as well as the increased choline-acetyl-transferase activity in rats fed alcohol for long periods (25). These phenomena have been observed in dogs (25) and rats (30, 34, 35). The concept that during the nonalcoholic stage there is an ethanol-evoked release of a pancreatic inhibitory peptide is supported by the observations of Staub et al (53) of an elevation of plasma pancreatic polypeptide. This peptide could exert its effects paracrinically (54). Similar reasoning could be extended to somatostatin and other peptides.

Undoubtedly, one of the major findings of the present series is the discordance of post-plateau secretory changes elicited by intravenous ethanol in NA and AF rats subjected to duodenal recirculation (Fig. 5). Indeed, the striking differences observed offer a clue to the intimate mechanism by which ethanol acts on the exocrine pancreas. BPS diversion or recirculation triggers different pathways of the duodeno-pancreatic reflexes (short, medium, and long) that link the neurons of the "duodenal autonomic brain" with those of the hypothalamic-bulbar centers, the "antral" and "celiac" autonomic nervous brains as well as the intrapancreatic ganglia (20, 28, 32, 33, 49, 50).

When BPS is recirculated into the duodenum, both a positive and a negative reflex is evoked and the final result is a consequence of their interplay. The positive reflex raises the intrapancreatic cholinergic tone and stimulates BPS, the negative reflex is elicited by the activation of nervous afferents in the duodenal mucosa, for example by trypsin and bile salts (short, medium, and long duodeno-pancreatic reflexes). These diminish impulses through the intrapancreatic ganglia as a consequence of decreased activity of the hypothalamic-bulbar nuclei and inhibition of the neurons of the intrapancreatic ganglia. The result is a fall of the intrapancreatic cholinergic tone and, thus, diminished "pancreon" activity. The latter phenomenon is also related to decreased release of CCK-PZ from the duodenal mucosa, a peptide which is a major stimulant to BPS in the rat (55–58).

When BPS is diverted from the duodenum, there appear to be alterations of the duodeno-pancreatic reflexes—first, a decrease of inhibitory impulses and, thus, facilitation of positive impulses through the intrapancreatic ganglia; second, a resulting change of activity of the hypothalamic-bulbar centers and enhancement of positive impulses from them as well as from the neurons of the "intermediate autonomic nervous brains." The final result would be increased intrapancreatic cholinergic tone and increased CCK-PZ release from the duodenal mucosa. This type of feedback control of BPS is peculiar to the rat (55–58). It is not present in dogs (59) and is uncertain in humans (60).

Under conditions of BPS duodenal diversion, when theoretically the restraining influence of negative duodeno-pancreatic reflexes on the "pancreon" and/or intrapancreatic ganglia is at its lowest level, an intravenous ethanol infusion evokes in both the NA and AF animals a slight increase of BPS. In contrast, under BPS duodenal recirculation, when hypothetically inhibitory duodeno-pancreatic reflexes are exerting their maximal influence on the intrapancreatic ganglia, the hypothalamic-bulbar centers, and the intermediate autonomic nervous brains, ethanol injection in the NA animal is unable to modify

TABLE

Changes Induced by Either IV Isotonic Sodium Chloride or Ethanol (2.0 mg/kg) on Concentration of Total Protein and Albumin in Bile-Pancreatic Secretion
(in mg/mL)

	N	Mean ± SD	*t*	*P*	% Difference
Total protein					
Preethanol	18	14.45 ± 0.81	1.89	NS	+14.4%
Postethanol	18	16.53 ± 0.74			
Total albumin					
Preethanol	18	4.18 ± 0.41	3.07	<0.005	+48.3%
Postethanol	18	6.2 ± 0.51			
Protein concentration					
Preisotonic saline	9	16.0 ± 1.24	1.42	NS	+3.94%
Postisotonic saline	9	17.2 ± 1.31			
Albumin concentration					
Preisotonic saline	9	5.05 ± 0.49	0.87	NS	+9.9%
Postisotonic saline	9	5.55 ± 0.40			

BPS parameters. On the other hand, in the AF rats, ethanol elicits an increase of volume (first post-plateau period) as well as protein concentration and output. Enhancement of the latter parameters in respect to those of the NA and the control animals is highly significant and progressively greater with time (Fig. 5).

Another hypothetical mechanism could be diminished capacity of CCK-PZ to release its own inhibitory hormone, PP, in the AF rats. This type of interplay is impaired in alcoholic animals, as reported in dogs by Schmidt et al (37, 38) and by us following topical lidocaine to the papilla of Vater as well by intravenous injection of the anesthetic, with or without atropine, in NA and AF animals (20).

Another striking finding of the present study was the increase of albumin level in the BPS following the intravenous ethanol infusion (Table, Fig. 6). This study was done only on NA animals but should be extended to AF rats. Ethanol-evoked rise of albumin levels in BPS suggests increased leakage of plasma protein from the pancreatic microcirculation across the duct epithelium into its lumen. These changes could also be related to the ethanol-evoked enhancement of the postganglionic nerve ending release of acetylcholine, VIP, and perhaps PHI (32, 33). It is known that these peptides elicit marked bloodflow changes in the gland (61).

An ethanol-elicited alteration of the duct epithelium barrier is also possible. The results recently observed by Reber (62) in cats indicate that ethanol, like aspirin, impairs the semipermeability of Wirsung duct epithelium, allowing passage of large molecules such as the enzymatic proteins from the duct lumen to the gland interstitium. Another recent finding by Bonting (63) implies ethanol-induced leakage of blood albumin into BPS in rabbits, that is, carbachol stimulates the secretion of protein and horseradish peroxidase in the pancreas. Histochemical analysis reveals that horseradish peroxidase enters the interstitial spaces of the pancreatic tissue and is present along basal and lateral plasma membranes of acinar and ductular cells. However, in the carbachol-stimulated gland, horseradish peroxidase is observed in the junctions between acinar cells more frequently than in the nonstimulated gland. Freeze fracture of the acinar cells indicates that the number of the tight junctional strands and the tight junction depth are slightly decreased following carbachol stimulation.

These findings suggest that cholinergic stimulation of the exocrine pancreas increases the permeability of the acinar cell junction to moderately large molecules. As we have previously shown that ethanol enhances the intrapancreatic cholinergic tone (5, 6, 11, 25, 30, 32, 33), it would be logical to conclude that increased albumin leakage into BPS evoked by alcohol infusion is related, at least in part, to facilitated passage via a paracellular pathway. Were those modifications also verified in chronically alcoholic animals, as predicted from previous studies (12, 54), it would clarify the pathogenesis of protein plugs and pancreatic stones in chronic calcifying pancreatitis.

A recent fascinating finding by Brugge et al (64) in humans agrees with our present finding that chronic alcoholics and alcoholics recovered from acute pancreatitis have increased trypsin secretion during phase II of interdigestive pancreatic secretion, a phenomenon accompanied by increased rate of duodenal contractions. According to these authors, a common mechanism might explain both changes. They suggest, as we have hypothesized in previous reports (5, 6, 9, 11, 12, 32, 33), that increased cholinergic stimulation of the duodenum and pancreas results in enhanced contraction of the duodenum and augmented pancreatic secretion in the interdigestive state.

These latter findings of Brugge et al (64) lend additional support to our hypothesis that ethanol exerts its effects on the "pancreon" units through an indirect mechanism mediated by the autonomic nervous system. Furthermore, there are several recent findings, with different protocols (54, 65), also in agreement with these postulations; for example, no alterations in protein synthesis have been observed in pancreatic cells suspended in an alcoholic incubation medium. Furthermore, cells from rats given alcohol by mouth for six weeks display protein synthesis similar to those in control rats.

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Graduate Training in Community Medicine at Mount Sinai:

The Development of the Master of Science in Community Medicine

Alan Silver, M.D., and Kurt W. Deuschle, M.D.

Abstract

This paper describes the philosophy, process, and outcome of the integration of independent study and classroom training with existing clinical and research experiences in The Mount Sinai Medical Center Department of Community Medicine's general preventive medicine and occupational medicine residencies leading to the creation of the Master of Science in Community Medicine.

Community medicine is medicine as it applies to population groups. Its domain was explicated more than twenty years ago by Jesse W. Tapp, M.D., and Kurt W. Deuschle, M.D.:

> Community medicine is the academic discipline that deals with identification and solution of health problems of communities or human population groups. The discipline, like internal medicine or pediatrics, has for its goal the solution of people's health problems. . . . However, community medicine considers people in groups or communities as well as individually, encompassing the traditional and relevant skills and knowledge of public health and preventive medicine along with the growing concern for the delivery of medical care. (1)

Since its inception in 1968, the Department of Community Medicine of the Mount Sinai School of Medicine of the City University of New York has been involved with the education of physicians in its discipline. The department has had residencies in general preventive medicine and occupational medicine since the early 1970s. It is one of only a handful of medical schools in North America that offers both programs (2). Occupational and general preventive medicine residencies in total constitute but 0.5% of all graduate training positions in the United States (3).

The purpose of these residencies is, first, to educate physicians in the application of the population aspects of medicine: behavioral science (anthropology, psychology, sociology), biostatistics and epidemiology, environmental medicine and occupational medicine, and medical care organization; and, second, to provide an integrated didactic, clinical, and research setting to enable trainees to gain skills and expertise in their specialty. The program is a medical-school-based entity for physicians that uses its clinical setting and community orientation as the focus for problem-based learning in preventive medicine (4).

This problem-based learning method is a direct extension of the traditional clinical training program in its purposeful weaving of didactic training and medical practice into a cohesive experience. In these programs, unlike most other residency programs, medical practice entails both ongoing clinical and research experiences and formal classroom training. This approach stresses the value of integrated didactic and practicum elements. The practicum components focus structured learning experiences on solving problems. The formal academic training provides both the reinforcement and the knowledge base for the clinical and research experiences.

In the 1970s and early 1980s, the department provided classroom experiences with a small series of lecture courses in epidemiology

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and environmental medicine, complementing more traditional grand rounds and special lecture formats highlighting other aspects of community medicine. It became apparent, however, that the increasing complexity of the field required more extensive classroom training for future specialists in occupational and general preventive medicine. In late 1987, the department and the Mount Sinai School of Medicine undertook the process of expanding the course work into a formal master of science degree, making it the first use of the school's charter to give a master of science degree. The intention was not to move toward creating a school of public health, but rather to build on the strong clinical history and resources of Mount Sinai to expand an academic program in community medicine firmly within a school of medicine.

Residencies in Occupational and General Preventive Medicine

To understand the context of the master's program, it is necessary to briefly outline the occupational medicine and general preventive medicine residencies. These two-year programs educate physicians in the application of population-based medicine for positions in environmental medicine, health care planning, clinical epidemiology, industrial medicine, clinical preventive services, and health services research. They are accredited programs of the Residency Review Committee in Preventive Medicine of the Accreditation Council on Graduate Medical Education and represent a major portion of the requirements for board eligibility.

Board eligibility in both residencies (under the aegis of the American Board of Preventive Medicine) takes a minimum of four years after completing medical school. All candidates must have had at least one year of clinical training, the so-called internship year; an academic year leading to a master's level degree or its academic equivalent; a second residency year focused on preventive medicine practice; and an additional practicum year in ongoing preventive medicine work, either through a fellowship, further course work, or a job.

Both programs share the educational goal of presenting a core curriculum in biostatistics and epidemiology, behavioral science, environmental medicine, and medical care organization. The occupational medicine program has further educational goals: to enhance clinical knowledge in occupational or environmental exposures and suitability for workplace employment; to impart knowledge and skills in toxicology, industrial hygiene, and environmental monitoring; and to teach aspects of occupational and environmental health regulations, law, and worker's compensation.

The general preventive medicine program emphasizes aspects of clinical preventive medicine skills in primary care settings and further training in health care planning, administration, financing, and health services research. Both programs foster initiative and leadership skills through the development of tailored research and field site projects, such as industrial work sites, the Centers for Disease Control, city and state health departments, and community health centers.

Although the board requirements for these two specialties require only an internship year as the hospital-based clinical training component, both Mount Sinai residencies have been fortunate to attract almost exclusively physicians who are already board eligible or board certified in a clinical field, such as pediatrics, internal medicine, or family medicine. This is, in part, due to the overall reputation of Mount Sinai and the resources available in the "campus" of New York City, but it is also due to the nature and structure of the programs.

Both programs seek to take advantage of their medical school settings to train clinicians in aspects of population-based medicine. This focus is slightly different from most preventive medicine residencies, which tend to be based in schools of public health. Public health school programs usually attract physicians who seek pure population-based careers and are less likely to use the stethoscope in the future. Both approaches are valid and needed, but each serves a different niche in the medical care world. A consequence of this philosophy is the structure of the didactic program in the two settings.

Public health school residencies generally schedule their academic and residencies practice years in sequence. The trainee spends one full year in school obtaining a degree and then goes on to a second residency year after the course work is completed. This effectively splits the academic year from the field residency year, making ongoing clinical or research activities almost impossible. Physicians who hope to continue clinical work, particularly in primary care, must give up all hope of continuity during the academic year.

The Mount Sinai approach has been to weave the academic and residency practicum through both years. Class work and clinical experiences are organized so they can occur throughout the

TRADITIONAL PUBLIC HEALTH SCHOOL PROGRAM

Year 1. Master in Public Health Degree (10 month year, 2 months vacation)

	Mon	Tues	Wed	Thur	Fri
AM	├── Master's Classes ──┤				
PM	├── Master's Classes ──┤				

Year 2. Field Practicum (10 month year, 2 months vacation)

	Mon	Tues	Wed	Thur	Fri
AM	├── Research or supervised experience in preventive medicine ──┤				
PM	├── Research or supervised Experience in preventive medicine ──┤				

MOUNT SINAI PREVENTIVE MEDICINE PROGRAM

Year 1 and 2 (11 month year, 1 month vacation)

	Mon	Tues	Wed	Thur	Fri
AM	Clinical work	├── Master's Degree (classes or thesis) ──┤		Research or thesis work	Clinical work
PM	Prev. Med. field work	├── Master's Degree (classes or thesis) ──┤		Research or thesis work	Prev. Med field work

Fig. Comparison of a program leading to a master's degree in preventive medicine at Mount Sinai Department of Community Medicine and a traditional public health school program.

residency program. Classes are clustered into one or two days a week, allowing ongoing clinical, field epidemiology, or other practicum experiences to be maintained throughout the residency. This allows a more direct reinforcement of the classroom with the practicum while still allowing for blocks of time in which the residents are free from clinical demands during the week. The net effect has been to attract the clinically oriented physician who has become interested in learning community medicine but wishes to maintain clinical activities (Fig.).

Although the combined academic field practicum format was obviously easier to do in the early 1970s when we offered fewer courses, the departmental faculty felt it was important to try to continue this arrangement. The master's program would continue to cluster courses, when possible, and maintain the flexibility of this format so as to attract clinically oriented physicians consistent with the department philosophy.

Master's Degree Objectives and Implementation Process

The curriculum for the master of science in community medicine is intended to meet two objectives:

To provide students with basic knowledge and skills in the component areas of preventive medicine:

- biostatistical principles and methodology
- epidemiologic principles and methodology
- planning, administration, evaluation, and economics of health care programs
- environmental hazards to health and principles of their recognition and control

- social, cultural, and behavioral factors in medicine
- applications of primary, secondary, and tertiary preventive principles and measures in medical and administrative practice.

To allow students to pursue an in-depth study of a selected topic in preventive medicine (the master's thesis).

The objectives are a direct result of guidelines set forth by the American Board of Preventive Medicine and the history of the two residencies. Prior to 1987, the residents typically carried out one or two ongoing field practicum projects which led to a report or publication in a peer-reviewed journal. What was needed was to translate these objectives into an expanded curriculum within the Mount Sinai School of Medicine and City University of New York (CUNY) system.

Critical to the development of the master of science program was a review of other master's programs, particularly the Master of Science of Community Health Program at the University of Rochester School of Medicine and Dentistry (personal communication, Dr. James Zimmer 1985 self-study report for accreditation review from the Council on Education for Public Health; reference 5). Meetings were held with the division chiefs within the department, with the associate dean for graduate education and the associate dean for university affairs of the School of Medicine, and at CUNY with the president of the Graduate Center and Dean's Council, and the dean for academic programs. These meetings led to the creation of a structure for the master of science program which was subsequently reviewed by the same individuals and by the Dean's Council at the Mount Sinai School of Medicine. In June 1988 the degree program was submitted to the deputy commissioner for higher education and professional education of the State Education Department in Albany, NY.

After a series of administrative reviews, further written communications between the State Education Department and Mount Sinai, and a request from the state to a number of master's programs in the New York City area for written comments on concept, curricular focus, and possible impact, the degree was formally approved and registered in 1989. The first graduation took place in 1990.

Master of Science in Community Medicine Program

The two-year degree program consists of 39–45 credits (each credit constitutes approximately 15 hours of class time), including 21 credits for required core courses, 12 credits for the required master's thesis, and 6–12 credits for electives. The core courses are in four areas: behavioral science, biostatistics and epidemiology, environmental and occupational medicine, and medical care organization (Table).

The behavioral science core covers aspects of medical anthropology and sociology, and use of behavioral science and health education techniques in the care of individuals and communities. The epidemiology and biostatistics core emphasizes basic study design, descriptive statistics, critical literature appraisal, multivariate analysis, and other techniques in epidemiology. The environmental and occupational medicine core covers aspects of toxicology, pathophysiology, environmental risk assessment, psychological aspects of health and work, environmental law, and environmental epidemiologic techniques. The medical care organization sequence emphasizes microeconomic and organizational theory, financing, and management skills as they apply to health care systems; cost-benefit and cost-effectiveness analysis, decision theory, health status indices, and quality-of-care measurements in medical care.

Elective courses can be chosen from offerings at the medical school, other CUNY programs such as the Baruch College program in health care management, the CUNY Graduate Center, or the Hunter College School of Health Sciences, or by special arrangement at other graduate schools in the New York City metropolitan area.

The master's thesis is an original research project predominantly done in the second year of the program. Students may choose a topic from any of the major areas in preventive medicine, such as environmental medicine, medical anthropology, or health economics. The thesis is under the tutelage of a project advisor and is reviewed by a thesis advisory committee. The paper can be based on primary or secondary data collection and is typically 25–50 pages in length.

The epidemiology and biostatistics sequence is given every year. All other courses are given in alternate years, with the exception of the basic environmental medicine course, which is given in a two-year bloc but with each yearly bloc given in alternate years. Since the courses are constructed so that none except epidemiology and biostatistics assumes prior knowledge of other courses, all core courses can be taken in a two-year program with minimum duplication of courses. There are typically twelve residents in the program at any one time and approximately six graduates in any

TABLE
Master of Science in Community Medicine Core Courses

Course	Number	Title	Credit
		Epidemiology and Biostatistics	
EPB	500	Applied Course in Clinical Epidemiology and Biostatistics	2
EPB	510	Biostatistics, Second Level	2
EPB	520	Epidemiology of Chronic Disease	1
		Behavioral Science	
BES	610	Culture, Health and Illness	1
BES	620	Principles of Behavioral Science in Clinical Medicine	1
		Medical Care Organization	
MCO	700	Health Care Economics Organization and Management	3
MCO	710	Health Services Research Methods and Policy Analysis	3
		Environmental and Occupational Medicine	
EOM	800	Fundamentals of Environmental and Occupational Medicine	6
EOM	810	Environmental and Occupational Medicine Case Studies	2
COM	900	Master's Thesis	12
		Electives	6–12
TOTAL			39–45

given academic year. Each course has only one section, and the residents spend much time together in the classroom. Other students and residents from Mount Sinai or other CUNY programs may take the courses, limited only by section size and the discretion of the individual instructor.

The core course faculty are all from the Department of Community Medicine and have backgrounds in anthropology, biometry, economics, epidemiology, environmental and occupational medicine, health administration, health education, pathology, clinical medicine, industrial hygiene, psychology, toxicology, and chemistry. The administration of the master's program is mainly performed by the education director for the Department of Community Medicine who, in turn, is responsible to the dean of the medical school. A program budget provides for payment to the course directors and thesis advisors. The budget was established using time accounts developed by the faculty (6).

Discussion and Summary

The Master of Science in Community Medicine was developed in response to a perceived need by the Department of Community Medicine chairman, the departmental faculty, the Accreditation Council on Graduate Education, and the departmental residents. It is the first master's degree granted by the Mount Sinai School of Medicine. The degree is part of general preventive medicine and occupational medicine training programs in which formal classroom work is incorporated directly in graduate training for physicians, one of only a few programs in the United States that do so.

We are finding that this concept, embracing a format that encourages ongoing clinical care, is attractive to physicians who wish to learn more population-based medicine while continuing in activities that maintain the traditional doctor-patient relationship. We have been fortunate, so far, to attract individuals from other medical institutions for full residency programs, and also for fellowships which allow them to continue work at their own hospital, clinic, or office while obtaining a degree. Other departments at the Mount Sinai School of Medicine have shared our interests and we have been able to develop joint programs.

For example, the current cohort of students includes pediatricians, internists, and a psychiatrist. The trainees are all active clinically and interact with students, housestaff, and faculty in both the ambulatory and inpatient settings at The Mount Sinai Hospital, North General Hospital, and the City Hospital Center at Elmhurst.

Their projects include the development and implementation of a community-based AIDS care system, the development of an East Harlem primary care network, the enhancement of primary care residencies at North General and the City Hospital Center at Elmhurst, and the understanding of the role of psychiatric comorbidity in the utilization of inpatient services.

At the core of this program is the belief that instead of attempting to expand the crowded undergraduate medical curriculum with courses that may not have meaning to medical students, one should instead expand the classroom format to graduates whose experiences have kindled the desire to have a broader framework.

At present the degree is only available to physicians, and the course content and structure can always be improved. We believe, however, that the Master of Science in Community Medicine is a contribution to the academic environment at the Mount Sinai School of Medicine of City University of New York and to the enhancement of health and medical care as envisioned by the medical school at its inception (7).

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Hodgkin's Disease in the Mesenteric Lymph Nodes in a Patient with Colon Carcinoma

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Abstract

We describe a patient in whom Hodgkin's disease affecting the mesenteric lymph nodes was discovered incidentally at laparotomy for carcinoma of the colon. The occurrence of Hodgkin's disease and colon carcinoma in the same patient is rare, as is Hodgkin's disease in the mesenteric lymph nodes. In cases in which Hodgkin's disease is discovered incidentally at laparotomy, staging is usually done by using computerized tomography and lymphangiographic studies.

THE INITIAL symptom of Hodgkin's disease is usually a painless adenopathy of peripheral lymph nodes above the diaphragm that may be associated with fever, weight loss, night sweats, pruritus, and alcohol-induced pain in the affected areas. Only about 3%–10% of patients have subdiaphragmatic disease (1), and the mesenteric lymph nodes are rarely involved (2). We describe a patient in whom Hodgkin's disease affecting the mesenteric lymph nodes was found incidentally during laparotomy for carcinoma in the ascending colon. The coexistence of Hodgkin's disease and colon carcinoma in the same patient is rare.

Case Report

A 65-year-old man with a history of coronary artery disease, chronic renal failure requiring dialysis, and chronic obstructive pulmonary disease had melena and a worsening anemia not characteristic of his renal failure. The patient was obese, but he had no abdominal masses, organomegaly, tenderness, or generalized or localized lymphadenopathy. The stool was positive on guaiac testing, but a rectal examination yielded normal results. The patient had no fever, abdominal pain, or change in bowel habits.

Colonoscopy revealed a friable, polypoid mass just distal to the cecum. The mass was approximately 4 cm in diameter and had several small ulcerations; a biopsy indicated a moderately differentiated adenocarcinoma. Exploratory laparotomy showed a carcinoma of the proximal ascending colon that grossly involved the serosa. There was no evidence of local or distant metastases. A right hemicolectomy with an ileotransverse colostomy was performed, and the patient tolerated the procedure well.

Pathological studies of the resected colon specimen showed a moderately to poorly differentiated adenocarcinoma of the ascending colon that had invaded the pericolic fat (Fig. 1). However, examination of the mesenteric lymph nodes in the surgical specimen revealed Hodgkin's disease of the mixed-cellularity and the lymphocyte-depleted types, with Reed-Sternberg cells (Fig. 2).

Postoperative abdominal and thoracic computerized tomographic (CT) scans showed a homogeneous liver and an unexplained area of lucency in the spleen. Lymph nodes in the hilar region of both lungs were mildly enlarged, the pericardium was thickened, and there was a small pericardial effusion. An examination of the

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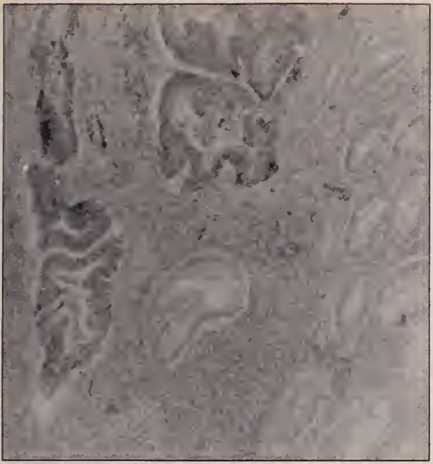

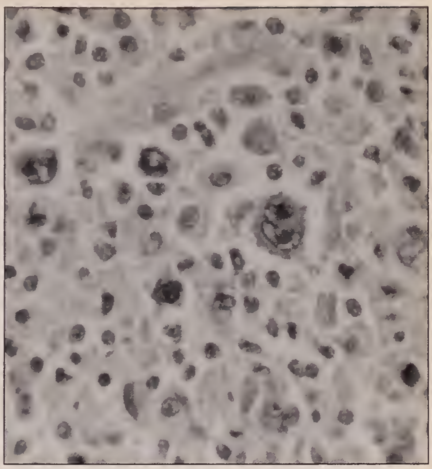

Fig. 1. Left Section of resected colon specimen showing moderately to poorly differentiated adenocarcinoma involving pericolic fat (hematoxylin and eosin, original magnification ×400). **Fig. 2. Right** Section of mesocolic lymph nodes showing mixed-cellularity and lymphocyte-depleted Hodgkin's disease with formation of Reed-Sternberg cells (hematoxylin and eosin, original magnification ×400).

bone marrow aspirate revealed no evidence of Hodgkin's disease.

The patient was given a diagnosis of stage $IIIA_s$ lymphocyte-depleted Hodgkin's disease, and he began to receive outpatient therapy with mechlorethamine, vincristine, procarbazine, and prednisone. He is currently doing well on the regimen and is scheduled to receive six cycles of the chemotherapy.

Discussion

Hodgkin's disease below the diaphragm occurs chiefly in older men (1). In a combined series, about 80% of cases of subdiaphragmatic Hodgkin's disease initially appeared as peripheral inguinal, femoral, or superficial iliac lymphadenopathy (3). Other patients with subdiaphragmatic Hodgkin's disease initially have an intraabdominal mass (3), a fever of unknown origin (4), splenic abnormalities (5), autoimmune hemolytic anemia, immune thrombocytopenia (6), an epidural mass, or extranodal lesions, including masses in the gastrointestinal tract (7).

Our patient was discovered to have Hodgkin's disease affecting the mesenteric lymph nodes during a laparotomy and resection of the colon for adenocarcinoma. He was subsequently found to have Hodgkin's disease in other sites. Hodgkin's disease in the mesenteric lymph nodes is rare and is seldom encountered incidentally at laparotomy (2). Most patients in whom the disease is found incidentally have an abdominal mass.

Synchronous primary lymphoma and colon carcinoma is rare, but cases have been reported by Cornes (8), Polk and colleagues (9), Barron and Localio (10), Mir-Madjlessi et al (11), Sugihara and co-workers (12), and Jaworski et al (13). One of the four patients described by Barron and Localio (10) was found, like our patient, to have lymphoma in mesenteric lymph nodes obtained during a colon resection for adenocarcinoma.

Barron and Localio (10) calculated the conditional probability that a patient with colon cancer has lymphoma as about 2%. The relationship between the two disorders is unknown, but several explanations for their coexistence have been proposed, including the genetic constitution of the patient and immunosuppression resulting from malignant disease (10). In most reported cases, including ours, the colon cancer is the presenting illness.

Our patient's subdiaphragmatic Hodgkin's disease varied from the mixed-cellularity to the lymphocyte-depleted type. Hodgkin's disease below the diaphragm usually is of the mixed-cellularity type (47.5% of cases) (14). Other patients with synchronous colon carcinoma and lymphoma have been found to have lymphosarcoma (8, 10), reticulum-cell sarcoma (8, 10), medium-cell follicular lymphoma (12), large-cell histiocytic lymphoma (11, 13), and mixed-cell follicular lymphoma (10).

When Hodgkin's disease is discovered as an incidental finding at laparotomy performed for another disorder, it is difficult to perform a staging procedure because of the limitations of the incision and the lack of preparedness of the surgical team (3). Moreover, the presence of the lymphoma is often revealed only by postoperative pathologic evaluations, and staging is then generally done with use of CT and lymphangiographic studies. A second laparotomy may be performed in younger, healthier patients, but usually not in older patients in poor health.

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Successful Retrieval of Fractured Tracheostomy Cannula by Flexible Fiberoptic Bronchoscopy

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We describe a case in which an outer cannula of a Jackson tracheostomy tube was successfully retrieved from the left mainstem bronchus approximately two months after the incident occurred. Aspiration was unnoticed by the patient, whose only symptom was increased production of purulent sputum. The aspiration had occurred when the outer cannula sheared off the metal faceplate while in position in the tracheal stoma. Our experience suggests that large foreign bodies can easily be retrieved from the tracheobronchial tree by flexible fiberoptic bronchoscopy and that with routine testing of equipment this complication may indeed be preventable.

Case Report

In June 1989 a 61-year-old black man sought medical assistance in an emergency room complaining of dizziness and mild tremulousness for several days. The patient had a history of generalized seizures dating from 1983 and was taking dilantin 100 mg orally three times daily. In September 1987 he underwent total laryngectomy and tracheostomy for squamous cell carcinoma of the pyriform sinus. He received radiation therapy postoperatively. One year later a roentgenogram of the chest revealed bilateral lower lobe nodules. Fiberoptic bronchoscopy and transthoracic needle aspirate were nondiagnostic. He was seen regularly in the Otolaryngology Clinic. During this time he was cleaning and changing the inner cannula of his Jackson tracheostomy tube every other day. The outer cannula and faceplate were cleaned and reinserted by the patient weekly.

Physical examination at the emergency room showed the patient to be a thin black man in no acute distress. He was afebrile, the pulse was 80 and regular, the blood pressure 140/90 mm Hg, and the respiratory rate 22. There was no adenopathy. An intact Jackson tracheostomy tube was in place. During the examination the patient coughed up moderate amounts of foul-smelling sputum. On chest examination the lungs were clear to auscultation and percussion. There was no organomegaly or clubbing. Neurological examination was significant only for nystagmus on lateral gaze.

Laboratory studies were significant only for a serum dilantin level of 37 μg/mL (normal 30 μg/mL). Because of this finding the patient was admitted to the hospital.

Routine admission roentgenogram of the chest revealed a radiopaque cannula in the left mainstem bronchus (Fig. 1). On further questioning the patient recalled removing the entire tracheostomy tube for cleaning approximately two months prior to admission and noticing that the outer cannula was missing from the faceplate. He felt well and presumed it had broken and dropped on the floor, though he was unable to find it. He then replaced it with a new tracheostomy tube. He reported no shortness of breath, fever, or wheezing but did admit to increased cough and secretions that were copious, thick, and foul-smelling.

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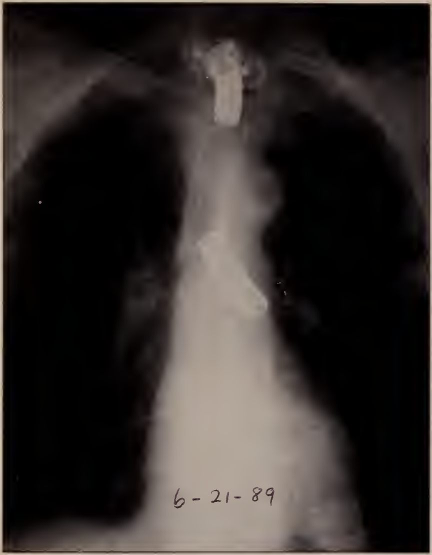

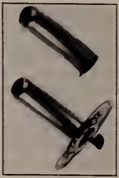

Fig. 1. Left Posteroanterior roentgenogram of chest showing outer cannula lodged in left mainstem bronchus. Fig. 2. Right Fractured outer cannula; beneath it, normal outer cannula with faceplate.

The patient was taken to the bronchoscopy suite and the Jackson tracheostomy tube in place was removed. Fiberoptic bronchoscopy was performed via the tracheal stoma using only lidocaine 2% instilled via the bronchoscope. After a moderate amount of thick, yellow, foul-smelling secretion was suctioned from the orifice of the left mainstem bronchus, the fracture edge of the outer cannula was easily visualized at the carina. There was marked edema and granulation tissue in the bronchial wall surrounding the tip of the cannula. The edge of the outer cannula was grasped with an alligator biopsy forceps. By slowly withdrawing the bronchoscope and forceps as a unit, the fractured cannula was dislodged and removed through the tracheal stoma (Fig. 2).

The fiberoptic bronchoscope was then reinserted for examination of the tracheobronchial tree, which was remarkable only for minimal bleeding at the site where the fractured cannula had been lodged. A repeat roentgenogram of the chest confirmed that the cannula had been removed.

Discussion

Fracture and aspiration of tracheostomy tubes has been reported in the surgical and anesthesia literature but has not received attention in the medical literature to date. Fractures of the inner and outer cannula from the faceplate of the metal Jackson tracheostomy tube occur, as does fracture along the body of the cannula. Bassoe and Boe (1) first reported the aspiration of a fractured metal tracheostomy tube in 1960. During a routine changing of the tracheostomy tube, it was discovered that a small fragment of the outer cannula was missing. A roentgenogram of the chest revealed that the fragment was lodged in the right mainstem bronchus. The foreign body was removed using a rigid bronchoscope while the patient was under general anesthesia.

Since that report, there have been 24 reported cases of tracheostomy tube fracture and aspiration occurring in 22 patients (2–13). Most of these have been isolated case reports. However, Gupta (2) has reported a series of nine patients over a period of eight years at his institution. Of the 25 fractures, 20 occurred in metal tracheostomy tubes, the rest in those made of polyvinyl chloride. Most of the defects occurred in the outer rather than the inner cannula. More than half (13/25) of the fractures occurred at the flange, or soldered junction between the cannula and faceplate. The rest involved the aspiration of small fragments of the body of the cannula. Seventeen (of 25) patients were asymptomatic, usually seeking medical care after having noticed a missing fragment during a routine tracheostomy change.

In a third (8/25), the aspiration went undiagnosed for anywhere from four days to eight years. Most of the patients in whom such a delay occurred had noted a missing segment of their tracheostomy tube; however, because they were asymptomatic, they did not suspect an aspiration.

Probably because of the curvature of the tubing and its large size, most of the cannulae lodged proximally. Cannulae were most commonly found in the mainstem bronchus (11/22 patients), left mainstem bronchus (4/22), trachea (4/22), and carina (2/22). Because of the hollow nature of the tubing, airflow remained unobstructed, perhaps accounting for the relative paucity of symptoms.

In all but two of the twenty-five fractures previously reported, general anesthesia was necessary for rigid-bronchoscope removal. In one case the aspirated cannula was just beneath the tracheostome and was removed under direct vision (2). In one instance, local anesthesia was induced and a flexible nasopharyngoscope was introduced to visualize the aspirated cannula while bronchoscopic forceps were passed through the stoma alongside the endoscope (3).

We believe the case reported here to be the first report of removal of an aspirated tracheostomy tube via a fiberoptic bronchoscope. Though some advocate proceeding directly to rigid bronchoscopy for large foreign body removal, we believe the fiberoptic bronchoscope can be used for quick and easy removal without the use of general anesthesia or the need for cervical spine hyperextension.

What causes the tracheostomy tube to fail is not entirely clear. Age of the tube is certainly not the sole factor, because several of the cases reported occurred in equipment only a few days old (7). It is possible that causes included

- Corrosion by alkaline tracheobronchial secretions of the metal alloy (1, 4, 6).
- Prolonged use.
- Repeated boiling (1, 5).
- Manufacturing defects.

As pointed out by Slotnick et al (3), one-piece construction of the metal tracheostomy tube would eliminate the fracture tendency at the flange; however, cost is considered prohibitive. Alternatively, equipment could be dated and discarded at intervals set by study of the durability of such equipment.

Summary

The fracture and aspiration of tracheostomy tubing is not rare. It may go unnoticed by the patient. The equipment is prone to shearing at the flange and fracture along its body.

Its integrity should be routinely tested, and a policy instituted for the discarding of old equipment. Fiberoptic bronchoscopy is advantageous in that it can be performed quickly and easily, it avoids general anesthesia, and it is more adaptable to foreign body retrieval than the nasopharyngoscope because of its forceps channel, through which varied retrieval instruments can be passed.

Acknowledgments

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Duplication of the Uterus with a Noncommunicating Functioning Uterine Horn

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Abstract

Incomplete duplication of the uterus with a functioning noncommunicating uterine horn is a rare developmental anomaly of the paramesonephric ducts. Although usually described in association with obstetric catastrophes, it has been reported recently in young women with gynecologic complaints. We describe a nulliparous patient with dysmenorrhea that had increased since menarche and a large pelvic mass. Surgical exploration revealed incomplete uterine duplication with a noncommunicating functioning uterine horn with a large hematosalpinx due to cryptomenorrhea. Inclusion of the anomaly in the differential diagnosis of young women with intractable, increasing dysmenorrhea and a pelvic mass will lead to prompt surgical intervention and obviate a catastrophic obstetric event.

DEVELOPMENTAL anomalies of the paramesonephric ducts are a well-known cause of both obstetric and gynecologic syndromes. The incidence of uterine malformation has been estimated to range from 1:500 to 1:2000 (1). Incomplete duplication of the uterus with a noncommunicating uterine horn is a very unusual anomaly. Its true incidence is unknown, and its diagnosis often depends on a high index of suspicion on the part of the clinician. However, it has been estimated to comprise approximately 7%–14% of all uterine anomalies (1–4). Usually it is diagnosed when the patient has an obstetric complication. Recently it has been described with increasing frequency in patients with gynecologic syndromes. We describe the case of a young patient with incomplete uterine duplication with a noncommunicating functional uterine horn who presented with dysmenorrhea and a pelvic mass.

Case Report

A 19-year-old, gravida 0, para 0 woman consulted a physician for the chief complaint of intractable, cyclically recurrent dysmenorrhea, which began at menarche. For the past year and a half she also had constant pain in the right lower quadrant. The chronology of her pubertal events was normal. Her history and review of systems was unremarkable. There was no history of maternal ingestion of diethylstilbesterol or any other teratogen.

Physical examination revealed an obese black woman in no acute distress. Her weight was 112 kg, her arm span 185 cm, and her pubis-to-floor span 95 cm. Her vital signs were normal. Positive physical findings were confined to the abdominal and pelvic examinations. The cervix appeared normal. The uterus was of normal size, mobile, and deviated to the left. A separate large, tender, semisolid mass filled the pelvis and rose to the level of the umbilicus.

Laboratory data included hemoglobin of 10.1

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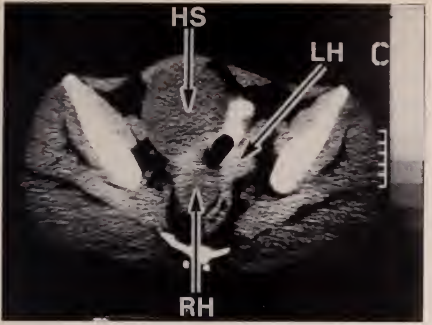

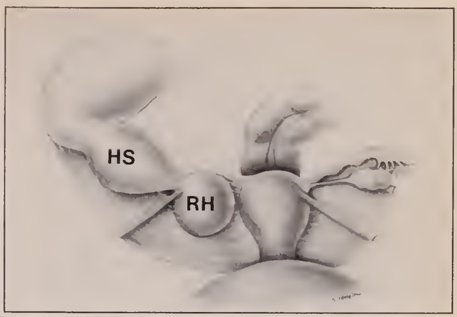

Fig. 1. **Left** Computerized axial tomography of the pelvis reveals left communicating uterine horn (LH), right noncommunicating horn (RH), and large hematosalpinx (HS). **Fig. 2.** **Right** Artist's rendition of noncommunicating right uterine horn (RH) with large hematosalpinx (HS) due to cryptomenorrhea.

mg/dL, a white blood cell count of 8,800, and a normal differential white blood cell count. The radioimmunoassay for the beta subunit of human chorionic gonadotropin was negative.

Pelvic sonography was interpreted as a normal uterus with multiple cystic structures, the largest 12 cm in diameter. Computerized axial tomography with oral and intravenous contrast demonstrated incomplete uterine duplication (Fig. 1). The left uterine horn communicated with the vagina, and the right noncommunicating uterine horn was continuous with a large hematosalpinx. The kidneys, uterus, bladder, and rectum appeared normal, and all other abdominal viscera were noted to be normal in their appearance.

At laparotomy, positive findings were confined to the pelvic viscera (Fig. 2). A large, tortuous hematosalpinx (36 cm long) arose from a right noncommunicating, functioning uterine horn. There was no free blood in the pelvis and no evidence of endometriosis. The ipsilateral ovary was normal in appearance. The left uterine horn was normal in external appearance and communicated with a normal-appearing left fallopian tube. The left ovary appeared normal.

The right hematosalpinx and right uterine horn were excised. Histologically the endometrium was atrophic and demonstrated acute and chronic inflammation. The hematosalpinx was long standing.

Postoperatively the patient had an uneventful course and when examined 6 weeks later she was completely asymptomatic.

Discussion

The paramesonephric ducts develop as invaginations of coloemic epithelium lateral to the mesonephroi. By seven weeks of fetal life, the edges of these invaginations fuse to form the paramesonephric ducts. The cranial ends of these ducts form the fallopian tubes, whereas the caudal ends burrow their way into the mesenchyme to fuse by nine weeks of fetal life, forming a T-shaped uterovaginal primordium. This gives rise to the epithelium and glandular structures of the uterus, whereas the stroma and myometrium are formed from the adjacent mesenchyme (5).

Incomplete uterine duplication with a noncommunicating horn results from unilateral partial maldevelopment along with failure of fusion of the paramesonephric ducts. The noncommunicating horn may be lined with functional endometrium; this endometrium may or may not correspond to the cycle phase of the communicating horn (6). The endometrium in the patient whose case is described here was atrophic, despite the obvious presence of accumulated menstrual products in the horn and ipsilateral tube. Because the hematosalpinx was long standing, the atrophic endometrium may represent the ultimate result of a once-functioning endometrium exposed to chronic pressure from many years of a blocked outflow tract.

The noncommunicating horn may alternatively consist of a nubbin of myometrium with no hormonally responsive endometrium present. It is usually found in conjunction with a patent ipsilateral fallopian tube and a normal ovary. It has, however, been described to occur in conjunction with an ipsilateral atretic fallopian tube (7).

The clinical presentation of incomplete uterine duplication with a functional horn is widely varied. Initially described by Mauriceau in 1699, it has since been reported by other investigators (2, 8–13). Many obstetrical cases have been described in the literature, and the clinical presentations have ranged from benign to catastrophic. The most dramatic presentation is that of rupture of the pregnant noncommunicating horn. Various other obstetrical presentations have included unsuccessful dilatation and curettage for early fetal demise, unsuccessful pitocin induction for late fetal demise (14), missed labor (8, 15), ectopic pregnancy (9, 11), and pelvic mass in pregnancy (8, 9, 11, 14, 15).

Although the actual incidence of pregnancy is not decreased, fetal wastage has been reported to range from 35% to 60% (13, 16). Most viable pregnancies result from implantation in the normal communicating horn. However, there have been case reports of fetal salvage following implantation in the rudimentary horn (10, 17).

Recently, gynecologic presentations have been reported when the anomaly was included in the differential diagnosis of endometriosis, chronic pelvic pain, pelvic mass, infertility, and dysmenorrhea (1, 2, 18–21). Prompt surgical intervention results in obviating catastrophic rupture of a noncommunicating horn in pregnancy.

The triad of dysmenorrhea beginning at menarche, increasing severity of dysmenorrhea with each menses, and a unilateral pelvic mass strongly suggests the diagnosis (20, 22, 23). Dysmenorrhea starting at menarche is highly suggestive of an anatomic rather than a functional derangement. Functional dysmenorrhea is usually experienced only after the onset of ovulation due to maturation of the hypothalamic-pituitary axis. Menstrual history in these patients reveals dysmenorrhea which usually begins shortly after menarche (20, 23). The increasing dysmenorrhea is due to the monthly accumulation of menstrual products within the noncommunicating functioning horn and often, as in the case described here, within the distensible ipsilateral fallopian tube. A unilateral pelvic mass, from 5 cm to 35 cm in diameter, is generally the only positive physical finding.

Hysterosalpingography in properly selected patients may be very useful in demonstrating a unicornuate uterus (4). However, the radiograph cannot definitively diagnose the presence of a noncommunicating functioning horn. It has been suggested that medialization of the communicating horn may suggest the presence of a noncommunicating horn joined to the communicating horn in its upper portion. To our knowledge, this report presents the first computerized axial tomogram of this anomaly. Although experience with nuclear magnetic resonance imaging in diagnosis of uterine anomalies is limited (24), this technique may be of value in the future.

Once the diagnosis is suspected, it is extremely important to thoroughly evaluate the upper urinary tract. Developmental anomalies of the paramesonephric ducts are often associated with anomalies of the kidneys and ureters. The reported incidence of major renal anomalies associated with incomplete uterine duplication with a noncommunicating horn ranges from 60% to 100% (2, 13, 25). The most common anomaly is renal agenesis ipsilateral to the noncommunicating uterine horn, ipsilateral pelvic kidney being the second most common anomaly.

Definitive diagnosis is made at laparotomy, at which time the noncommunicating uterine horn is extirpated. Ipsilateral salpingectomy should be performed if the tube is irreversibly damaged by chronic distension with menstrual blood. Consideration may be given to implantation of the fallopian tube into the contralateral uterine horn if that procedure is feasible; as in any uterotubal implantation procedure, the potentially increased risk of postoperative ectopic pregnancy must be acknowledged, and the patient counseled and managed accordingly. The ipsilateral ovary should be carefully evaluated and its position noted. Malposition of the ovary above the pelvic brim has been reported with developmental anomalies of the paramesonephric ducts (26).

In summary, incomplete uterine duplication with a noncommunicating functioning uterine horn must be considered in the differential diagnosis of patients who have intractable dysmenorrhea that increases in severity from menarche and a unilateral pelvic mass. An increased level of suspicion on the part of the obstetrician-gynecologist will lead to definitive diagnosis and surgery for this anomaly prior to pregnancy. In this way the serious sequelae that often follow pregnancy in a noncommunicating uterine horn will be averted.

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The Formulary

Bernard Mehl, D.P.S., editor

Ganciclovir:

Approved and Investigational Uses for the Treatment of Cytomegalovirus Retinitis

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GANCICLOVIR (Cytovene, Syntex Laboratories, Inc.), a parenterally administered acyclic nucleoside analog, is currently the only agent approved for commercial distribution by the Food and Drug Administration for the treatment of cytomegalovirus (CMV) retinitis in immunocompromised individuals. Its exact role in the treatment of this viral infection continues to evolve as investigational antiviral agents (foscarnet), colony-stimulating factor (granulocyte macrophage colony stimulating factor), and routes of ganciclovir administration (oral, intravitreal injection) are studied and increase in availability.

This review briefly describes CMV retinitis as it occurs in patients with AIDS, then focuses on the mechanism of action, pharmacokinetics, current therapeutic role, and some recently described investigational uses of ganciclovir.

CMV Retinitis in Patients with AIDS

At least 5%–10% of patients with AIDS develop clinical evidence of CMV retinitis (1). Although occasionally CMV retinitis is the AIDS-defining illness, it is more commonly identified in a patient months to years after AIDS is diagnosed (1). Untreated unilateral CMV retinitis often progresses to bilateral ocular disease and, because viremia is common in patients with AIDS, may involve other organs (1, 2).

Ganciclovir

Mechanism of Action. The primary mechanism of the anti-CMV action of ganciclovir involves the selective inhibition of viral DNA polymerase by ganciclovir 5′-triphosphate, following the intracellular phosphorylation of ganciclovir by host-cell kinases (3). CMV may induce the production of these enzymes, as infected cells display elevated levels of ganciclovir 5′triphosphate when compared with uninfected cells (4). Ganciclovir triphosphate is a competitive inhibitor of viral DNA polymerase and, because it can be directly incorporated into viral DNA, can terminate DNA elongation (3).

Pharmacokinetics. Following intravenous administration to patients with normal renal function, ganciclovir displays dose-independent pharmacokinetics over a range of 1.6 mg/kg–5.0 mg/kg. A single 5 mg/kg dose in such patients results in a mean peak plasma level of 8.3 mcg/mL at the end of a 1-hour infusion, and 0.56 mcg/mL 11 hours after the start of the infusion (4). Notably, the IC_{50} (the concentration of drug required to reduce plaque formation by 50%) from a sample of 54 CMV isolates ranged from 0.1 to 2.75 mcg/mL (5).

Data describing the distribution of ganciclovir are limited. At autopsy, ganciclovir concentration ratios (organ tissue : heart blood) were 100%, 91%, 482%, 37.6%, and 92.7% in the lungs, liver, kidney, brain, and testes, respectively (6). Aqueous and vitreous humor ganciclovir concentrations were respectively 0.4 and 0.6 times the simultaneous plasma concentration 2.5 hours after intravenous administration (7). Ganciclovir does cross the blood-brain barrier. Cerebral spinal fluid concentrations following intravenous

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TABLE 1

Manufacturer's Recommended Ganciclovir Induction and Maintenance Dosages in Patients with Impaired Renal Function

Creatinine Clearance (mL/min/1.73 sq m)	Ganciclovir Dosage (mg/kg)	
	Induction	Maintenance*
≥80	5.0 q 12 hr	50%
50–79	2.5 q 12 hr	50%
25–49	2.5 q 24 hr	50%
<25	1.25 q 24 hr†	50%

Adapted from ref. 13.

* 50% = 50% of induction dosage.

† In hemodialysis patients, not to exceed 1.25 mg/kg every 24 hours. Daily dose should be given after dialysis.

administration average 41% (range 24%–67%) of the corresponding plasma drug concentration (8).

The elimination half-life in serum for patients with normal renal function (calculated creatinine clearance of ≥80 mL/1.73 M^2 per minute) is 2.5–3.6 hours. Such patients should receive ganciclovir induction doses of 5 mg/kg every 12 hours for 14 to 21 days. Total body clearance of ganciclovir linearly correlates with creatinine clearance, so dosage adjustment is required for patients with decreased creatinine clearance. Dosage guidelines for induction treatment are provided in the Table; note particularly that dosage modifications begin at creatinine clearance of less than 80 mL/min. No drug metabolites aside from the phosphorylated (activated) intracellular moieties are recognized in humans (7). Following intravitreal injection, limited data indicate that the elimination half-life from the vitreous humor is approximately 13.3 hours (7).

Approved Use for CMV Retinitis. Efficacy data submitted to the Food and Drug Administration included the pooled results from 254 patients with CMV retinitis and AIDS (4). The treatment group was compared to 61 untreated historical controls. The former group most commonly received 5 mg/kg of ganciclovir twice daily. Improvement or stabilization of CMV retinitis was reported in 56% and 26%, respectively, of treated patients, whereas only 0% and 3% of controls, respectively, had a similar response.

Regarding virologic response, in another group of 121 patients receiving induction treatment who had at least one positive baseline CMV culture, cessation of CMV viremia or CMV shedding in urine or throat secretions occurred in 92% of patients. Urine, blood, and throat cultures became negative in a median time of 8, 8, and 7 days, respectively (4).

Maintenance therapy (25–35 mg/kg per week, as 5 mg/kg daily or 6 mg/kg 5 days each week) has been shown to slow the rate of CMV retinitis reactivation following induction therapy. In a group of 121 patients, those receiving no maintenance therapy or low-dose therapy (10–20 mg/kg per week) had a median time to relapse of 37 and 31 days, respectively. Also in those groups, the percentage relapse free at 120 days was 14% and 0%, respectively. In comparison, those patients receiving 25–35 mg/kg per week (n = 70) had a median time to relapse of 145 days, and the percentage relapse free at 120 days was 58% (4).

The most frequently reported adverse reactions associated with ganciclovir use are granulocytopenia (40%) and thrombocytopenia (20%) (4). Neutropenia also occurs during zidovudine (Retrovir, AZT) therapy; therefore, concomitant, prolonged ganciclovir and zidovudine treatment can be problematic. For example, when zidovudine 600 mg/day and ganciclovir maintenance therapy were coadministered, Hochster et al. reported that 82% of patients (n = 11) required modification of their drug therapy, as the median time to toxicity (primarily hematologic) was 5 weeks (range 2 to 40 weeks) (9).

Ongoing Investigations. The combination of intravenous ganciclovir and granulocyte macrophage colony stimulating factor (GM-CSF) is being compared to ganciclovir alone in phase II studies by the AIDS Clinical Trials Group (ACTG). Preliminary data from 25 patients indicate that although GM-CSF decreases the occurrence of neutropenia in ganciclovir recipients, severe thrombocytopenia (<25,000 platelets/mm^3) and eosinophilia (>35% total leukocytes) occurs more frequently than in those receiving ganciclovir alone (10). Notably, three patients receiving the combination of ganciclovir and GM-CSF were able to tolerate zidovudine.

Intravitreal injections of ganciclovir are being studied in patients who are unable to tolerate systemic ganciclovir therapy (ACTG 085). Utilizing this route of administration, Heinemann reported on 7 patients treated with induction (200 mcg × 6 over 18 days) and maintenance (200–300 mcg weekly) injections (11). Two patients were dropped from the study within the first two weeks, one because of severe intractable thrombocytopenia and the other because of retinal detachment. The remaining 5 patients all demonstrated an initial response, whereas untreated control eyes all demonstrated disease progression. Complications in the treatment group included two relapses, one of which responded to an increased weekly intravitreal dose of 300 mcg, and one case of *Staphylococcus epidermidis* endophthalmitis.

Although the bioavailability of ganciclovir is only 6%–9%, studies of orally administered ganciclovir are being performed (ACTG 127). Oral drug administration eliminates the risks of infection, catheter care needs, and drug administration difficulties encountered when immunocompromised patients require daily infusions and have permanent indwelling catheters. Follansbee et al. studied the pharmacokinetics and safety of oral ganciclovir, 1000 mg every 8 hours in 8 patients with CMV retinitis and AIDS (12). On day 14 of this regimen they reported a maximum serum ganciclovir concentration of 1.20 mcg/mL and a trough of 0.82 mcg/mL. Data describing the efficacy of oral ganciclovir are presently unavailable.

Drug Costs

A 500-mg vial of ganciclovir costs the Mount Sinai Department of Pharmacy $29.00. A typical 14-day course of induction therapy costs $812 ($58 per day). The drug costs for a daily maintenance infusion is $29.00.

Conclusion

Initial induction treatment with ganciclovir is effective in up to 80% of AIDS patients with CMV retinitis. Lower-dose maintenance treatment can further prevent disease progression, although relapse is not uncommon. Reinduction is often effective in such patients. Many of the factors that now complicate CMV therapy, such as neutropenia, intravenous-catheter-related infections, CMV resistance, and inability to treat HIV in patients receiving CMV therapy, are currently being addressed by alternate routes of administration and alternative therapeutic agents and regimens. Information on the ACTG trials available at Mount Sinai Medical Center, including ACTG 129, a study which compares ganciclovir with foscarnet, is available (212-241-8902). Information on the use of ganciclovir is also available from the Mount Sinai Drug Information Center (212-241-6619).

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Student Corner

Patient Satisfaction with Diagnostic Cardiac Catheterization:

Ambulatory vs. Inpatient Performance

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Abstract

In a combined retrospective and historical cohort analysis, 72 patients at The Mount Sinai Hospital were studied to assess satisfaction with diagnostic cardiac catheterization and coronary arteriography performed as an ambulatory procedure (40 patients) and as an inpatient procedure (32 patients). A composite questionnaire designed to measure patient satisfaction was generated by the method of summed ranks, a common method of pooling aspects from several sources. Ten psychosocial dimensions of patient satisfaction were explored to determine if any difference existed between the ambulatory-patient population and the inpatient population. The ambulatory-patient group had a higher total mean satisfaction score than the inpatient group (4.01 vs. 3.60, $p < .001$). Analysis of the specific dimensions showed that the ambulatory group had mean satisfaction scores higher than those of the inpatient group in convenience of procedure (4.12 vs. 3.13), continuity of care (3.83 vs. 3.42), technical quality (4.85 vs. 4.05), interpersonal aspects of communication (4.53 vs. 4.01), physical environment (4.14 vs. 3.18), and global satisfaction (4.71 vs. 4.25). These differences were statistically significant using the two-tailed t test ($t > t_{.05,70} = 1.994$). These data suggest that cardiac catheterization performed as an ambulatory procedure yields greater satisfaction than when performed as an inpatient procedure. This fact, in combination with prior published conclusions that ambulatory cardiac catheterization is more cost effective and has a statistically similar complication rate, supports the recommendation that this procedure be performed as an ambulatory procedure.

CARDIAC CATHETERIZATION has become an important diagnostic tool in the investigation of patients with cardiovascular disease. It was developed 40 years ago to help physicians evaluate valvular heart disease, but today, most of the catheterizations are performed with coronary arteriography to evaluate coronary artery disease (CAD). Approximately 800,000 coronary arteriograms are performed each year in the United States (National Center for Health Statistics). Recently, the most significant change that has taken place with diagnostic cardiac catheterization does not involve the technique itself, but rather the setting in which the procedure is performed (1, 2).

Diagnostic cardiac catheterization has been utilized in the evaluation of clinical disease to definitively identify the type, location, and severity of the lesion and the presence or absence of associated conditions. Before corrective procedures such as angioplasty or the newest laser interventions can be performed, diagnostic cardiac catheterization must be implemented.

Over the past decade, outpatient cardiac catheterization has been increasingly recognized as an alternative to inpatient cardiac catheterization. The benefits of outpatient catheterization, including the potential for increased patient compliance, greater family interaction, less time lost from work, and increased convenience, make it

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an attractive alternative to the inpatient procedure (1, 3, 4). Furthermore, the complication rates do not seem to be increased with the outpatient procedure, and the significantly lower costs provide an argument in favor of outpatient performance. However, in order for the argument to gain strength, the salient features of patient satisfaction must be more rigorously analyzed.

Although diagnostic cardiac catheterization is clearly beneficial to the patient and performing it on an ambulatory basis may be cost efficient without increasing complication risks, the question of patient satisfaction has not been addressed. It is conceivable that a patient could feel better knowing he or she is close to the immediate care of the hospital. Conversely, admission may increase the patient's anxiety. In this age of rising health care costs and reactive cost containment efforts, it is imperative not to sacrifice the patient's satisfaction because of third-party reimbursement plans.

Our retrospective study has probed several of the dimensions that are most influential in establishing patient satisfaction. Our findings will ideally have two major objectives: to justify the trend toward ambulatory performance of cardiac catheterization by discussing a factor neglected in previous literature, patient satisfaction; and to gather information which could be used as a basis for initiating a prospective randomized study intended to identify and modify these dimensions so that improved patient satisfaction with ambulatory cardiac catheterization can be achieved.

There is little controversy concerning the technique used in performing diagnostic cardiac catheterization; both Sones' brachial cutdown and Judkin's femoral approach are widely accepted. The question whether the procedure should be performed in an ambulatory or an inpatient setting, however, has not been adequately answered. Previous reports concerned with this question evaluate only two variables: comparative complication rates and comparative costs. Analysis of these two factors alone provides support for the ambulatory procedure (1–14). A neglected component is how satisfied patients are with the procedure.

With the exception of Block (1) and Fighali (2), all the studies discussing cardiac catheterization review complication rates only within the inpatient or the outpatient group, but not between the two groups. This is probably due to the fact that outpatient diagnostic cardiac catheterization and coronary arteriography were in their infancy. The figures for complication rates in outpatients and inpatients are remarkably similar, but only Block's and Fighali's results are significant because the two groups are analyzed within one study. Despite this, most physicians accept that there is not a statistically significant difference in complication rates between outpatient and inpatient groups (1, 2, 4, 10–12, 14).

In terms of hospital-related costs and charges, ambulatory catheterization is significantly more cost effective than inpatient catheterization (1–3, 5–8). One may intuitively expect that less time in the hospital translates into money saved. Levin (8) surveyed data on economic aspects of coronary arteriography and found that if the two-day average hospital-bed occupancy is eliminated, cost per individual for coronary arteriography of $2000 could be lowered by 12.4% or $248. The cost advantages of performing cardiac catheterization and coronary arteriography on an ambulatory basis is even more obvious in Fighali's study (2). The hospital-related costs for ambulatory cardiac catheterization were 26% less than for the inpatient procedure. The average cost per outpatient was $774; per inpatient (two-day semiprivate room) it was $1050. Fighali concludes that "outpatient cardiac catheterization provides significant financial savings" to the hospital and, ultimately, to the patient (2).

Purpose of Study. Previous comparisons of outpatient and inpatient cardiac catheterization and coronary arteriography consider only two components of advantageousness: complication rate and cost effectiveness (1–14). It is our intent to address patient satisfaction as a third component, either neglected or assumed in earlier reports but never substantiated. We attempt to determine whether ambulatory cardiac catheterization patients and inpatients differ in level of satisfaction with the procedure. If a difference does not exist, prior reports were not premature in recommending outpatient cardiac catheterization based solely on complication rates and cost effectiveness. If a difference does exist, however, patient satisfaction should be further examined to determine where improvements can be made. Specifically, anxiety, expectation, interpersonal aspects of care and communication, and convenience as dimensions of patient satisfaction are explored.

Materials and Methods

Population and Setting. The patient population was selected from a consecutive series of 131 patients who underwent elective cardiac catheterization at The Mount Sinai Hospital in New

York City between January and September 1989, 63 as inpatients and 68 as outpatients. We were able to contact 75 of the original 131 by telephone; two of the inpatients refused to participate, and one patient's recollections were too poor to be included. The ultimate population sample was 72. Since it is important to include only those patients who were truly candidates for either the inpatient or the outpatient setting, patients were excluded if their condition mandated inpatient care, because they had severe valvular disease (notably aortic stenosis), recent congestive heart failure, unstable angina, coronary bypass surgery following catheterization, or renal insufficiency. All patients included in the study underwent diagnostic catheterization for presumed diagnosis of coronary artery disease, stable angina, positive exercise stress test, or chest pain syndrome. The degree of disease was evenly distributed among both groups (Table 1).

The population sample was divided into 40 outpatients (ambulatory) and 32 inpatients (day of admission service, DAS). The decision on the setting for the procedure had been made by the personal physician. The mean age in the ambulatory (AMB) group was 56.4 years (range 29–77 years), in the inpatient (DAS) group, 62.6 years (range 38–82 years). There were approximately twice as many men as women in both the AMB (2.1:1) and DAS (2.2:1) groups (Table 1). Nationally, the sex ratio for this procedure in 1987 was 1.6:1 (data from the National Center for Health Statistics), slightly less than in our study.

Overall, the AMB and DAS groups corresponded well on ethnicity. Employment was also considered because it was felt that procedure-related days lost from work or planned activities would influence satisfaction. Sixty percent of the AMB group (24/40) and 59.4% of the DAS group (19/32) were currently employed; the remainder in each group were either unemployed or retired (Table 1). Eighty-five percent of the AMB group and 84% of the DAS group had a high school education or better. With respect to cohabitation, 22.5% (9/40) of all the AMB patients and 21.9% (7/32) of the DAS patients lived alone. In our study, 22.5% of the ambulatory group, as compared to 25% of the inpatient group, lived more than one hour travel time from The Mount Sinai Hospital.

In summary, we believe that the two groups, AMB and DAS, are well matched along all baseline characteristics and that the population is representative of all patients who are candidates for ambulatory catheterization (Table 1).

TABLE 1

Demographic Characteristics, 72 Patients Undergoing Elective Cardiac Catheterization at The Mount Sinai Hospital January–September 1989

Variable	Ambulatory (40 pts)	Inpatient (32 pts)	Total
Travel time to hospital			
<15 min	7	6	13
<1 hour	24	18	42
>1 hour	9	8	17
Live alone			
Yes	9	7	16
No	31	25	56
Degree of disease			
1 Vessel	5	5	10
2 Vessel	5	4	9
3 Vessel	7	7	14
Left main	4	2	6
Nonobstr	9	5	14
Unknown	10	9	19
Age			
<30 yr	1	0	1
30–50 yr	13	5	18
51–70 yr	20	18	38
>70 yr	6	9	15
Mean age	56.4	62.6	59.2
Range	29–77	38–82	29–82
Season			
Winter (Dec–Feb)	4	9	13
Spring (Mar–May)	20	6	26
Summer (Jun–Aug)	16	10	26
Fall (Sep)	0	7	7
Sex			
Male	27	22	49
Female	13	10	23
Ethnocultural group			
White	31	28	59
Black	5	2	7
Hispanic	3	1	4
Asian	1	1	2
Marital status			
Never married	4	0	4
Currently married	29	20	49
Previously married	7	12	19
Education			
Less than H.S.	6	5	11
High School	17	18	35
College	11	4	15
Graduate	6	5	11
Employment status			
Employed	24	19	43
Unemployed	3	1	4
Retired	13	12	25
Gross annual family income			
<$10,000	2	6	8
$10,000–<$50,000	6	13	19
$50,000–<$100,000	9	2	11
>$100,000	5	6	11
Not reported	18	5	23

Methods. A combined retrospective analysis and historical cohort was selected for the study design. Although a prospective study would have been ideal for reducing bias, it would not have generated a large enough sample population in the seven days designated for data collection. The retrospective component of the study allowed for a substantial increase in the sample size (72 elective cardiac catheterization patients).

The historical cohort component of the study analyzes the patients' satisfaction with elective cardiac catheterization and coronary arteriography. Patients were not asked to participate until seven days after the procedure. Patients with diagnosed one-vessel, two-vessel and three-vessel coronary artery disease or stable angina who received elective catheterization of the left side of the heart at The Mount Sinai Hospital between January and September 1989 were chosen consecutively for the study. Cases were included only if one of four designated cardiologists were the attending physician. Anonymity and confidentiality were maintained throughout the study.

Each subpopulation (AMB and DAS) of the sample population was studied independently to determine levels of satisfaction with the procedure. Technically, the procedure is performed identically in both settings. The only variable is the length of time following the procedure that the patient remains in the hospital.

The instrument used for the data collection was a questionnaire derived by the method of summed ranks (15) from the Client Satisfaction Questionnaire (CSQ-8) (16), Patient Satisfaction Questionnaire (PSQ) (17), Evaluation Ranking Scale (18), and other multiple sources (19, 20). The questionnaire is composed of 43 questions (31 5-point Likert-type; 12 open-ended) probing 10 different psychosocial dimensions of patient satisfaction. A telephone interview, following an introductory letter to describe our purpose, was selected as the most efficient means for generating a sufficient response rate. The questions were previously tape recorded and then played back to the patient in order to standardize and eliminate the bias caused by voice intonation and inflection during questioning. The patients' charts were reviewed to match patients for history, sociodemographics, and extent of disease and also to determine whether they satisfied the criteria for inclusion and exclusion.

The two subpopulations were compared using two-tailed *t* tests to assess statistical significance for patient satisfaction.

Results

Of the study sample of 72 patients, 4 had undergone the procedure in both settings and were unanimous in their conviction that the ambulatory procedure is significantly more "satisfying" than the inpatient procedure.

The results (Table 2) show that the overall total mean satisfaction score for the ambulatory patient group was significantly higher than that for the inpatient group. Further analysis of each dimension comprising the satisfaction questionnaire for any differences between the two groups showed statistically significant differences in six categories: convenience of procedure, continuity

TABLE 2

Mean ± SD for CQS Dimensions

Dimension	No. of items	Inpatient Mean ± SD	Ambulatory Mean ± SD	*t*	*P*
Convenience of procedure	5	3.13 ± 0.57	4.12 ± 0.49	7.92*	<.001
Continuity of care	2	3.42 ± 0.73	3.83 ± 0.63	2.56*	<.02
Postprocedure recovery	3	4.03 ± 0.65	4.11 ± 0.70	0.50	
Technical quality	2	4.05 ± 0.94	4.85 ± 0.28	5.11*	<.001
Interpersonal communication	5	4.01 ± 0.69	4.53 ± 0.38	4.06*	<.001
Education understanding	3	4.13 ± 0.74	4.46 ± 0.67	1.98	
Expectation	2	3.38 ± 0.54	3.51 ± 0.63	1.56	
Anxiety	7	3.11 ± 0.52	3.02 ± 0.67	1.03	
Physical environment	3	3.18 ± 0.95	4.14 ± 0.69	4.96*	<.001
Global	4	4.25 ± 0.76	4.71 ± 0.48	5.05*	<.001
Total satisfaction	36	3.60 ± 0.38	4.01 ± 0.32	4.97*	<.001

* Statistically significant.

of care, technical quality, interpersonal aspects of communication, physical environment, and—perhaps most important—global satisfaction.

The two groups, however, did not differ significantly in four of the dimensions comprising patient satisfaction: postprocedure recovery, education/understanding, expectation, and anxiety.

To the question, "Who made the decision to have the procedure done on an Ambulatory/Inpatient basis?" 82% responded that their physician decided. However, when prompted with the followup question, "Why was that particular choice made?" fewer than 50% stated a reason. Hence, the majority of patients did not know the physician's reasons for the decision.

In assessing the correlation between age and satisfaction, we found that age was strongly correlated with mean satisfaction ($r = 0.972$, $t = 34.82$, $p < 0.001$), indicating that older patients are more satisfied than younger patients. This is supported by various articles reviewed by Ware (21). However, when comparing the relative ages of the two groups, it is apparent that the ambulatory group's mean age is statistically lower than that of the inpatient group (56.4 years vs. 62.6 years, $t = 2.12$, $p < 0.05$).

Finally, the number of cardiac catheterizations performed appears to rise and fall and the choice of setting appears to reverse seasonally. In the spring and summer, 52 procedures were performed, 36 ambulatory (69%) and 16 inpatient (31%). In the winter, the trend reversed; of 13 procedures, only 4 (31%) were ambulatory, vs. 9 (69%) inpatient.

Discussion

The overall satisfaction difference between inpatient and outpatient experience with diagnostic cardiac catheterization is statistically significant and allows us to reject our null hypothesis. In interpreting the mean scores for overall satisfaction, both the ambulatory and inpatient group achieved values greater than 3 (AMB, 4.01; DAS, 3.60). Since scaled values in the questionnaire rank 5 as most satisfied, 3 as average, and 1 as most dissatisfied, it becomes apparent that both ambulatory and inpatient groups were satisfied with their catheterization experience. This is consistent with published reports that "overall satisfaction with hospital care is usually high, as is satisfaction with medical care" (15, 22).

Pascoe has defined patient satisfaction as "a health care recipient's reaction to salient aspects of his or her experience" (23). Care must be exercised not to prematurely conclude that a patient is satisfied without first identifying and examining the constituent elements of satisfaction. Unfortunately, "researchers rarely differentiate which dimension of satisfaction is being measured and frequently only total or global satisfaction is used" (24).

Of the ten dimensions probed (Table 2), six were shown to be statistically higher in the ambulatory population. The higher degree of convenience established for the ambulatory setting can be explained most convincingly by pointing out that all but a select few of patients in the ambulatory population missed less than one day of work or planned activities. Furthermore, most of the ambulatory patients left the hospital by early afternoon, allowing easy and rapid transition back home the same day. As many patients indicated, the outpatient procedure does not require that family members or friends make an additional trip back to the hospital the next morning to pick up the patient. Many of the outpatients had a common suggestion: the hospital should consider a home-to-hospital and hospital-to-home transport service for elderly patients, to avoid a hospital stay simply because a patient is old and cannot get to and from the hospital.

One might assume that the level of satisfaction with the physical environment would be the same for the two groups. This is vastly incorrect; we found a statistically significant difference between the mean scores of the two groups in this dimension. The ambulatory patients' recovery room is distinct from that of the inpatients. Whereas the inpatients proceed for the night to their hospital room, where up to three other patients may already be present, the ambulatory patients go to a four-bed transition unit, where they are in the company of patients sharing the same experience. The ambulatory patients tended to rate cleanliness, noise level, and privacy as much more satisfactory than did their inpatient counterparts. This may be due to the fact that they are aware of the temporariness of their stay or that the transition unit is truly superior with respect to these variables. The disparity between scores was even greater for the night following the procedure. Ambulatory patients cited that they "should be" satisfied with the cleanliness, noise level, and privacy, since they were in their own beds.

Continuity of care is a dimension that convincingly supports ambulatory catheterization over inpatient catheterization. Again, the difference between the two groups' scores was statistically significant. The differences may be attributable to the length of time between when a patient is told that he or she needs catheterization and when the procedure is actually performed. It could be rationalized that the inpatients would have to wait longer for the procedure because the date-limiting factor would be a hospital bed following the procedure. Since the ambulatory patients were not dependent on a bed, they did not have to wait, and their procedure date was expedited. When this dimension was analyzed further, however, it was determined that the duration of time that patients had to wait from entering the hospital to the time they were taken to the catheterization room was the sole determinant in this category. Apparently, ambulatory procedures are scheduled to be the first or second performed on a particular day. The benefits are twofold: (a) the procedure begins and therefore ends earlier, allowing the ambulatory patients to go home earlier; and (b) the patient spends less time anticipating the procedure, which is anxiety provoking and may be detrimental to satisfaction levels.

The technical quality of care and the interpersonal aspects of communication were two dimensions on which the difference between the ambulatory and inpatient groups was statistically significant. Because the same team of cardiologists cared for both populations, it is likely that the nursing staff was most influential in generating this difference. The inpatients go directly to their rooms on the medical floors or cardiac unit to settle in for the night. Here, they are exposed to the floor nurses, who must attend to a larger number of patients and a multitude of responsibilities. Ambulatory patients proceed to the designated ambulatory catheterization recovery room, where a higher nurse-to-patient ratio allows more concentrated and personalized care. This enhanced patient-nurse interaction influences the patient's perception of care and may translate into increased satisfaction (as reflected in the scores) (6, 25).

No statistical significance was found for differences in anxiety levels of the two groups. The possibility exists that anxiety may be exacerbated by any hospital admission. If a patient is hospitalized, he or she may assume that he must be more severely ill than someone else undergoing the same procedure as an outpatient. Empirically, one might expect the anxiety of inpatients to be higher than the anxiety of outpatients. However, admission to a hospital after cardiac catheterization that follows the experience at worst of myocardial infarction and at best chest pain may actually allay fears by providing the potential for swift emergency care, and may tend to lower the anxiety of the inpatient, making it statistically similar to that of outpatients. The other plausible mechanism for the insignificant difference in the two groups' scores might be that anxiety levels in the outpatient group are higher than intuitively suggested. The outpatients, by definition, leave the hospital on the day of the procedure, often before the cardiologists have an opportunity to interpret the coronary cinegrams. Several days may elapse before the patient hears the definitive results from their private physicians, whereas inpatients are usually informed of the definitive results before being discharged.

No statistically significant difference was found in the scores on the education and understanding dimension. This may be attributable to the fact that both groups are given a pamphlet on catheterization written in lay terms. Both groups are given an opportunity to ask questions of the same physicians about the procedure and are given a consistent explanation. Similarly, post-procedure and recovery scores, specifically referring to the week following discharge from the hospital, were remarkably close in both the outpatients and inpatients. (After discharge, both patient populations are presumed to be at home.) The fact that the same physicians perform the same procedure at the same facility for both groups explains why the two scores were similar.

Interesting data was also generated as a result of three open-ended questions. To the question of who was most influential in selecting the setting for catheterization, the most popular response was the doctor. Therefore, it is the physician's responsibility to consider all variables in choosing the setting for the catheterization, including both medical and nonmedical indications, such as season, lifestyle, and distance from hospital.

A direct correlation between an older patient's age and higher satisfaction level is often described as a potential confounding factor (21). In our study, however, age cannot be implicated as a confounding factor, since the ambulatory group, whose satisfaction level is higher than the inpatient group, actually has a lower mean age. This indicates that it is the outpatient or ambulatory setting, not an artifact of age, which is contributing to increased satisfaction.

The data and results generated by our study establish convincingly that patient satisfaction with cardiac catheterization is significantly higher in the ambulatory than in the inpatient population. The most convincing support, however, is supplied by the observation of a small subset of patients in our study. Four male patients in the ambulatory group had previously undergone the procedure as inpatients at the same hospital and thus represent the only true comparative evaluation of inpatient and outpatient cardiac catheterization, since they alone experienced the procedure in both settings. All four were unanimously more satisfied with the ambulatory setting. No study, to the authors' knowledge, has been undertaken in which the population sample consists entirely of patients catheterized in both the ambulatory and inpatient setting and whose condition at the time did not mandate one setting over the other. This design may perhaps generate the most powerful data for settling whether outpatient or inpatient performance of the procedure is truly more satisfying.

Conclusion and Recommendations

The results of our study enable us to reject our null hypothesis that there is no difference in levels of satisfaction with ambulatory and inpatient performance of diagnostic cardiac catheterization. Hence, in addition to complication rates and cost effectiveness, patient satisfaction must be factored in as support for ambulatory over inpatient cardiac catheterization.

Our analysis probes deeper than previous literature by delineating the different dimensions of patient satisfaction, not simply stating whether or not patients were "satisfied" (1–14).

Since the trend toward ambulatory cardiac catheterization is inevitable, those dimensions of patient satisfaction not found to be statistically different, including education and understanding, expectation, and anxiety, should be the focus of more rigorous analysis. By identifying and modifying these dimensions, enhancement of patient satisfaction and justification for ambulatory cardiac catheterization on grounds additional to the known benefits in cost and complication rates will be achieved.

In view of the greater patient satisfaction with the outpatient procedure established in our retrospective study, we recommend a prospective randomized study be conducted to support or refute our findings. The population should consist of patients who have been catheterized in both settings, ambulatory and inpatient. Although these patients will probably be more severely ill, as suggested by multiple catheterizations, they will nonetheless be able to express satisfaction or dissatisfaction with a particular setting. Until such a study is conducted, it may be premature to generalize our conclusions.

Additional studies should be conducted with factor analysis of the questions comprising each dimension we identified, to establish the appropriateness and the reliability of those questions.

Finally, we urge that all physicians involved in the recommendation of diagnostic cardiac catheterization for a particular patient do so after careful consideration of time of year (winter vs. nonwinter), physical limitations, psychological state, social factors, and preference of the patient.

Methodologic Limitations

1. The questionnaire asks patients to remember the procedure, and the feelings, time, convenience, and so on associated with it. Some patients had just experienced the procedure only a few weeks earlier, others had to remember an experience up to nine months old. The recall levels of the two subpopulations, outpatients and inpatients, may not be comparable. There may be a generalized and variable degree of forgetting, or there may be some pattern of forgetting within a particular group.

2. The cluster of questions comprising each dimension may not be a valid predictor of the dimension. Although factor analysis would be the most appropriate way to determine if the questions are indeed valid, time constraints prevented us from performing such a detailed analysis.

3. Our questionnaire was derived by pooling dimensions and questions from several sources. Unfortunately, our questionnaire's validity and reliability is unpredictable due to its hybrid origin. It may turn out to be more valid, equally valid, or less valid than the source questionnaires.

4. Time constraints jeopardized the content validity of our questionnaire because no pretesting was performed. There was no focus group, nor was there a formal pilot study.

5. Although we taperecorded the questions on the questionnaire, bias may still be inherent in that the responders were aware that a healthcare provider was listening to their answers.

6. The potential for acquiescence response set, the tendency of the responder to agree with statements of opinion, may have influenced our results (17, 26).

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